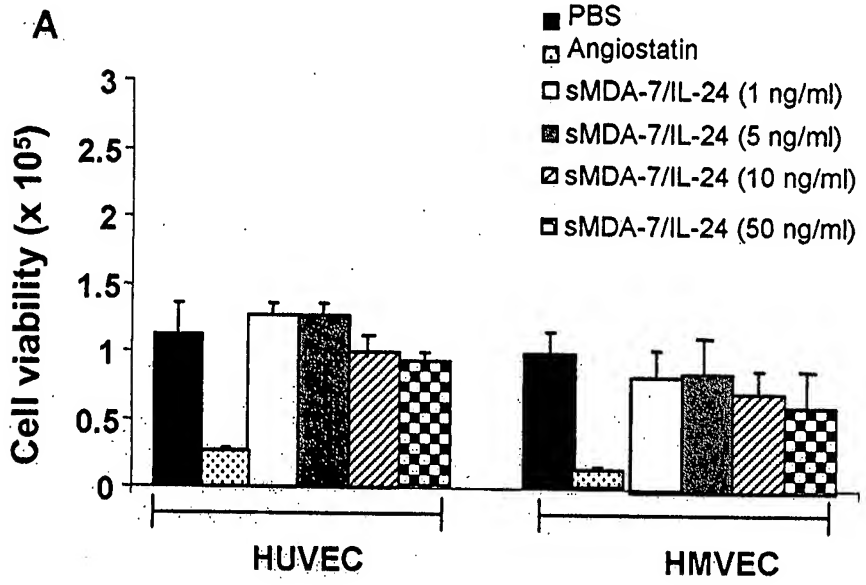
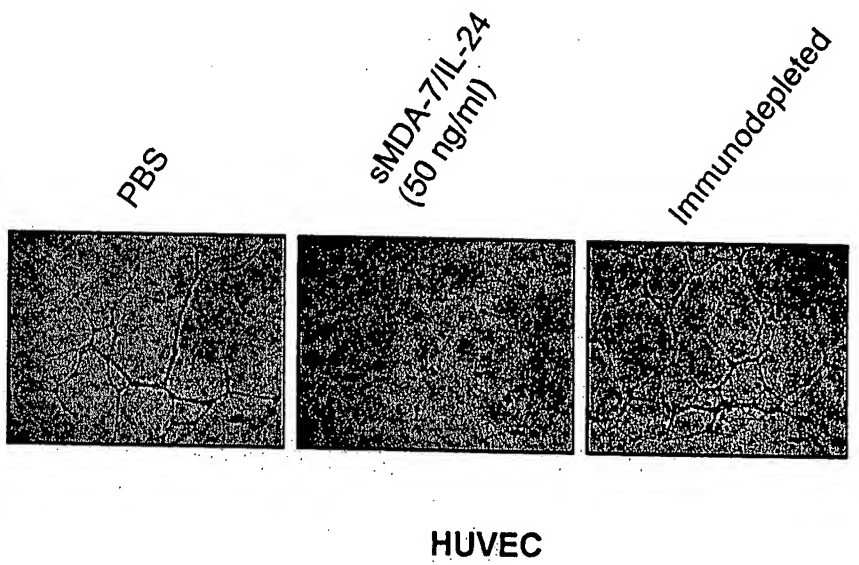
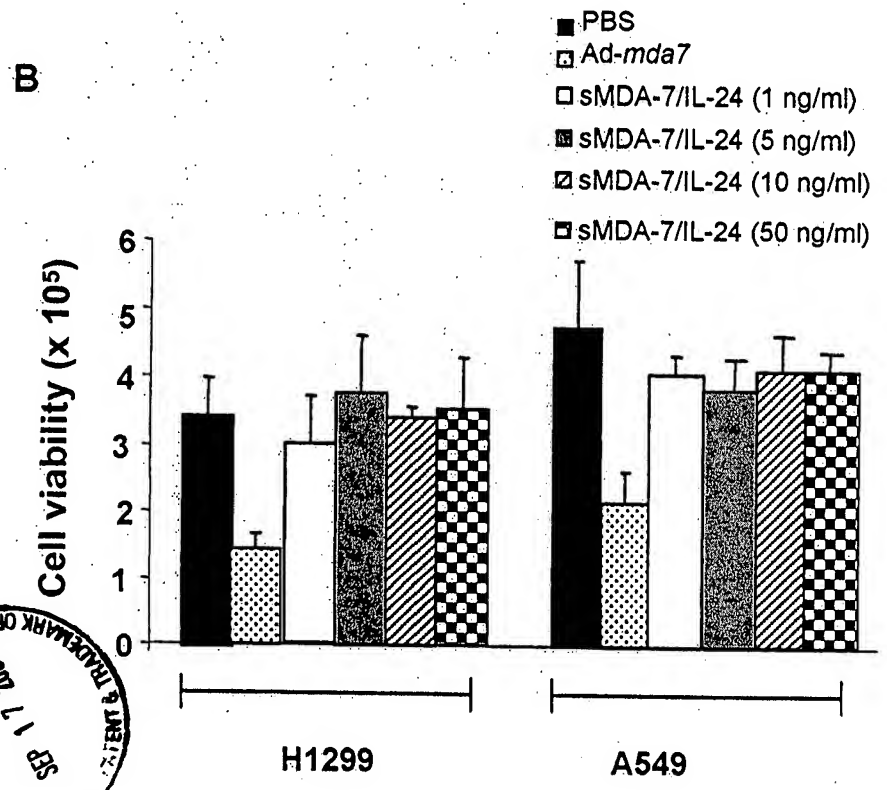
BEST AVAILABLE COPY







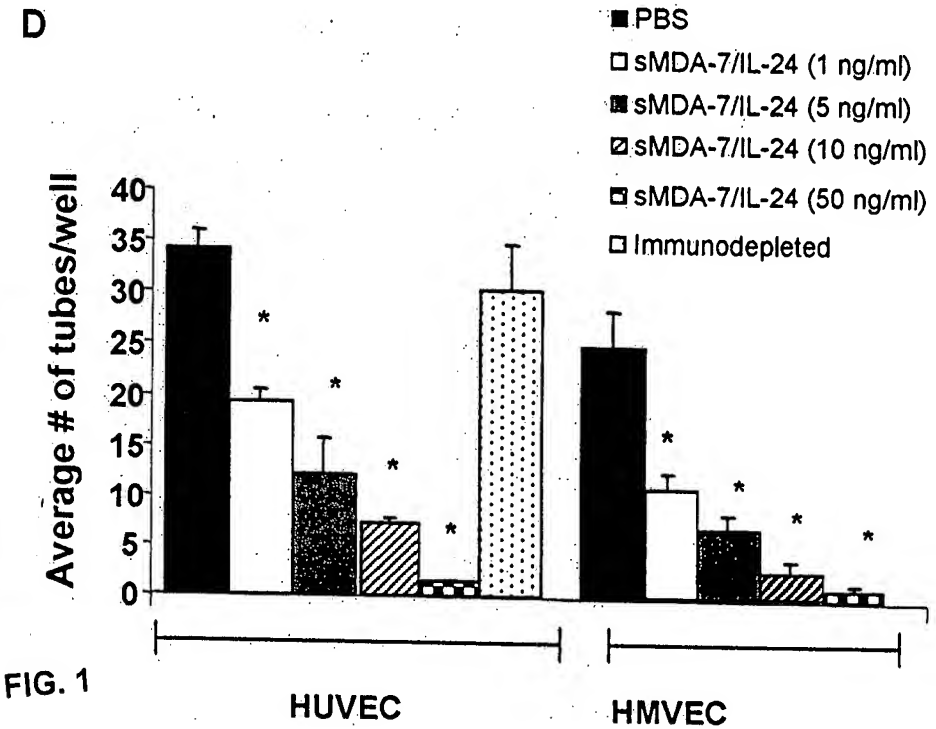


FIG. 1

OIPE JC79 SEP 17 2006 TRADEMARK OFFICE

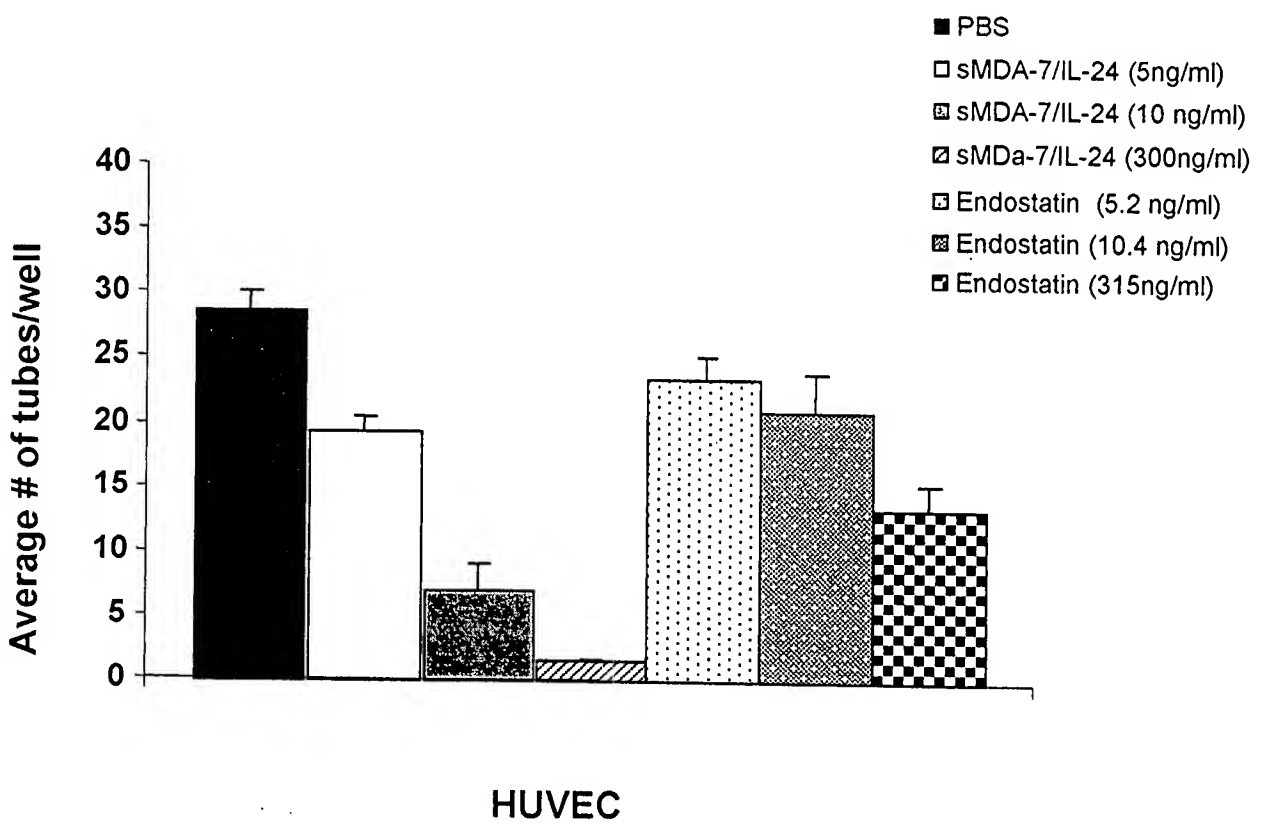

PBS
sMDA-7/IL-24 (5ng/ml)
sMDA-7/IL-24 (10 ng/ml)
sMDa-7/IL-24 (300ng/ml)
Endostatin (5.2 ng/ml)
Endostatin (10.4 ng/ml)
Endostatin (315ng/ml)
Average # of tubes/well
40
35
30
25
20
15
10
5
0
HUVEC

FIG. 2

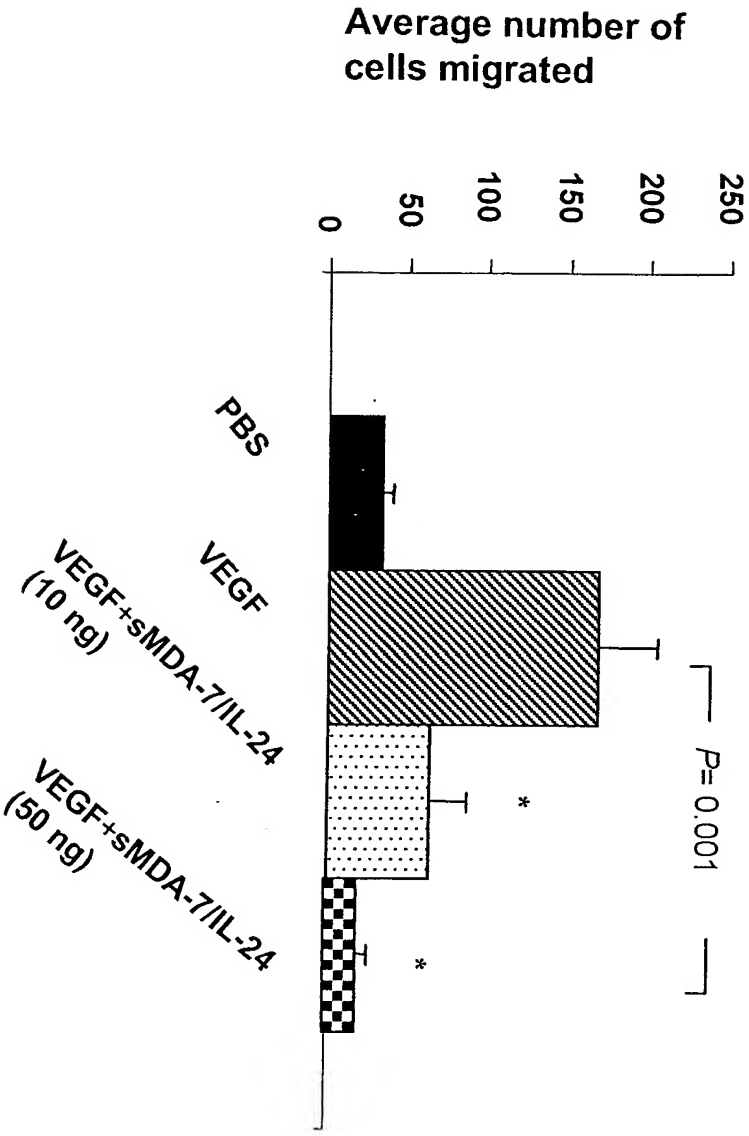

Average number of cells migrated
0
50
100
150
200
250
PBS
VEGF
VEGF+sMDA-7/IL-24 (10 ng)
VEGF+sMDA-7/IL-24 (50 ng)
*
*
P= 0.001

FIG. 3

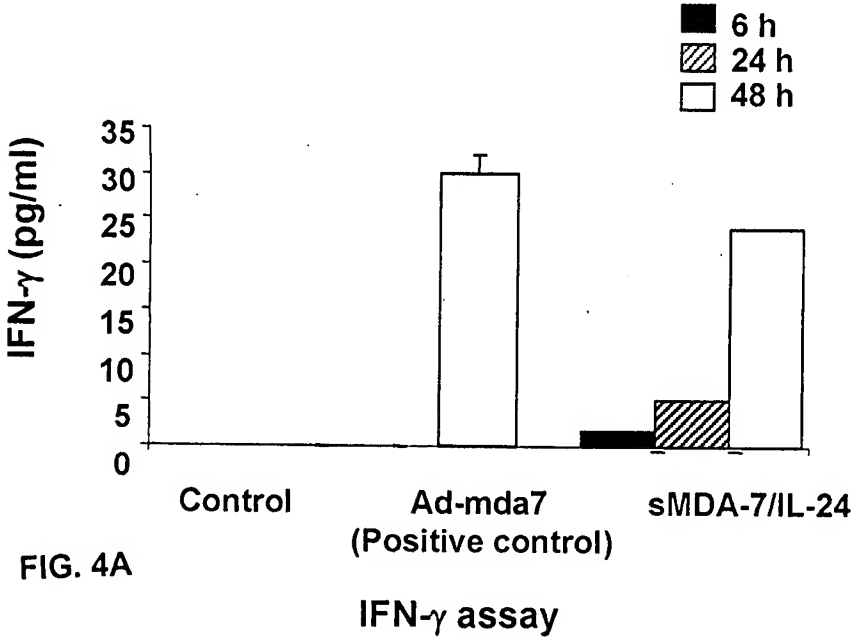


FIG. 4A

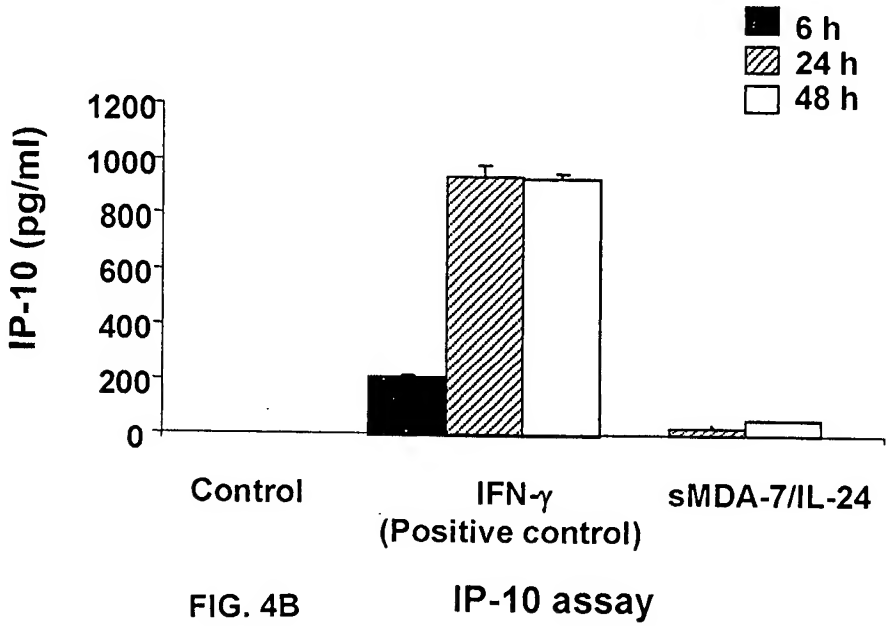


FIG. 4B

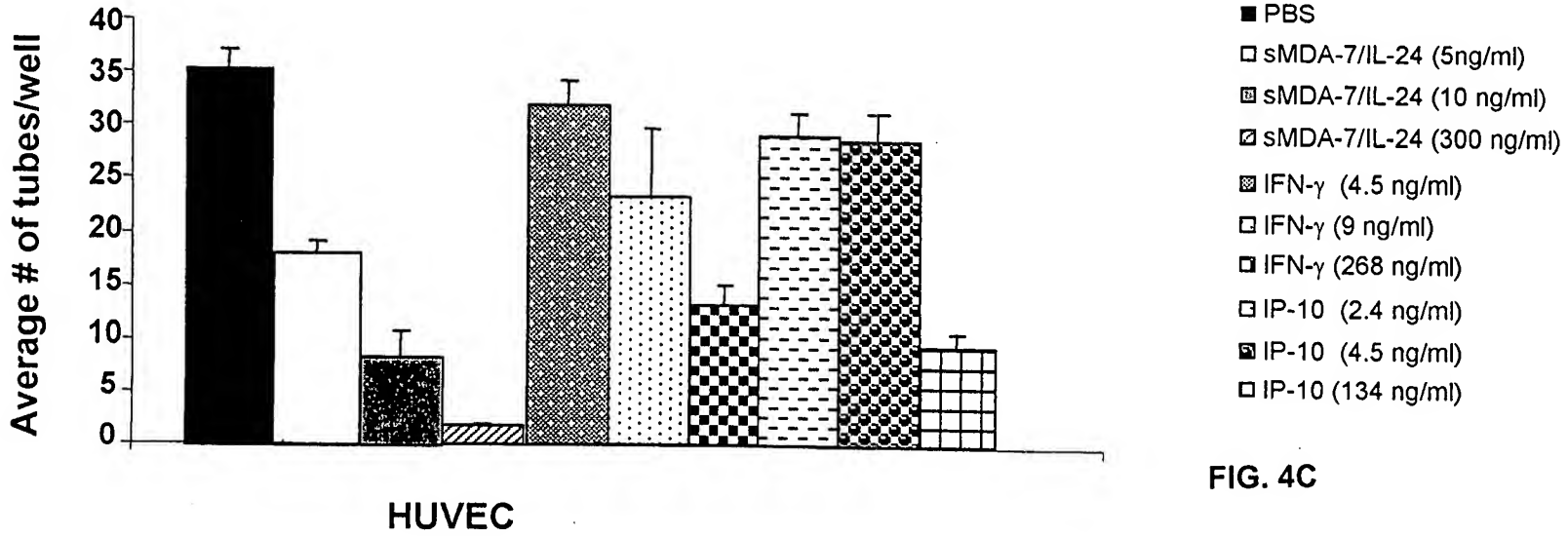
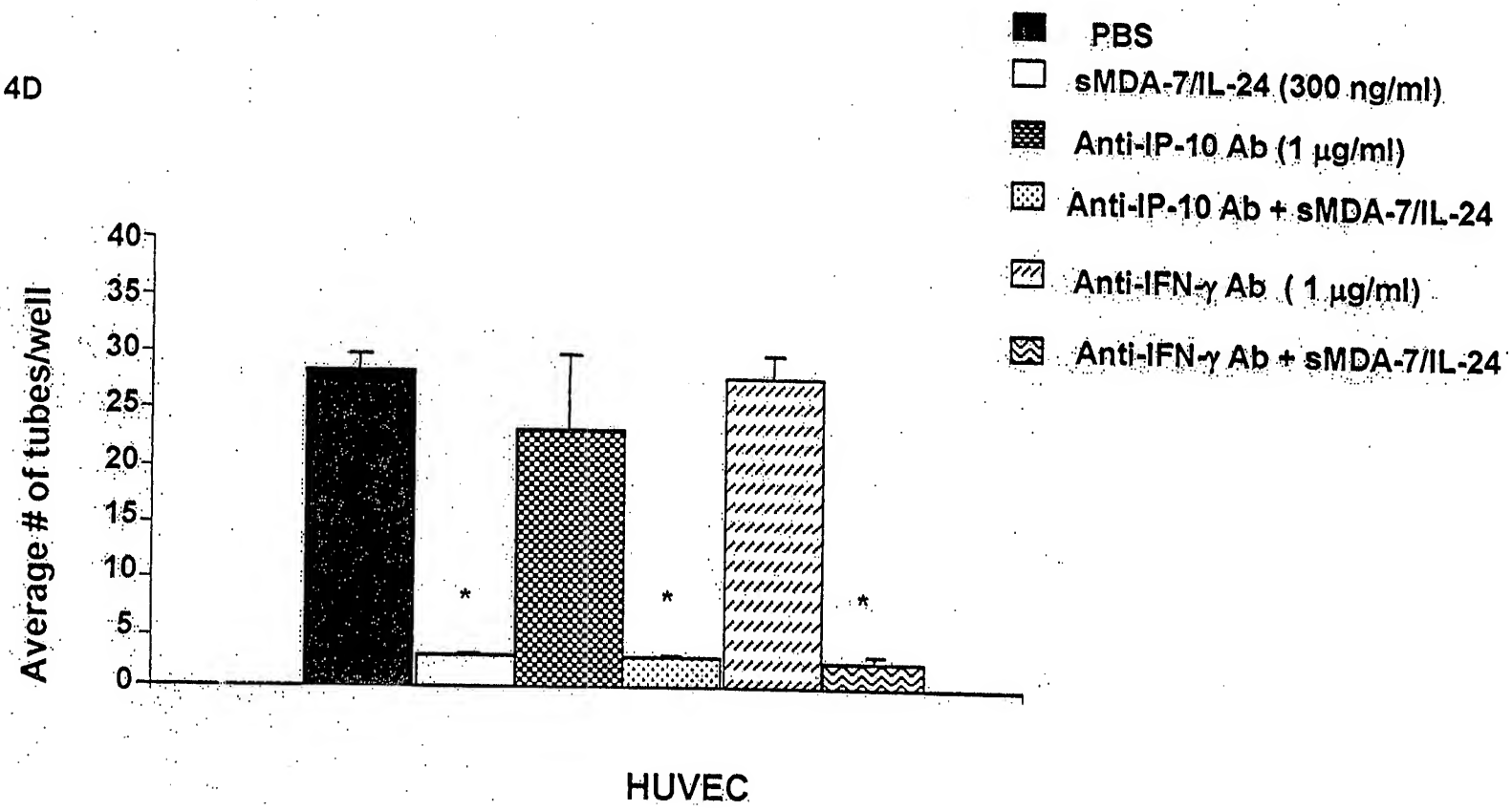


FIG. 4C

FIG. 4D


PBS
sMDA-7/IL-24 (300 ng/ml)
Anti-IP-10 Ab (1 μg/ml)
Anti-IP-10 Ab + sMDA-7/IL-24
Anti-IFN-γ Ab (1 μg/ml)
Anti-IFN-γ Ab + sMDA-7/IL-24
Average # of tubes/well
40
35
30
25
20
15
10
5
0
*
*
*
HUVEC

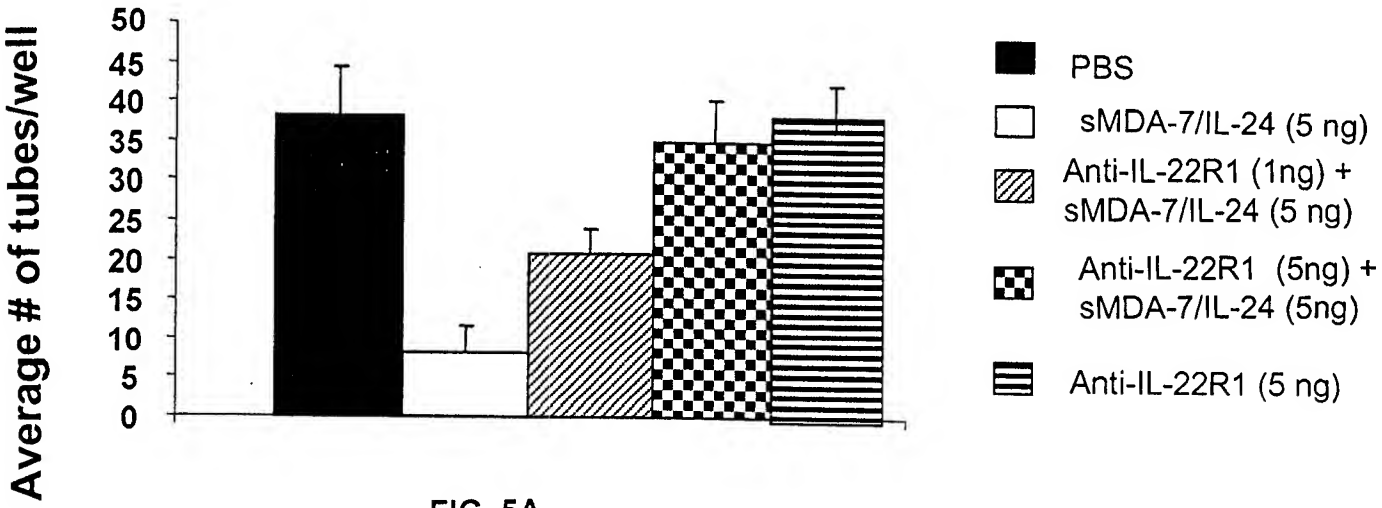

Average # of tubes/well
50
45
40
35
30
25
20
15
10
5
0
PBS
sMDA-7/IL-24 (5 ng)
Anti-IL-22R1 (1ng) + sMDA-7/IL-24 (5 ng)
Anti-IL-22R1 (5ng) + sMDA-7/IL-24 (5ng)
Anti-IL-22R1 (5 ng)

FIG. 5A

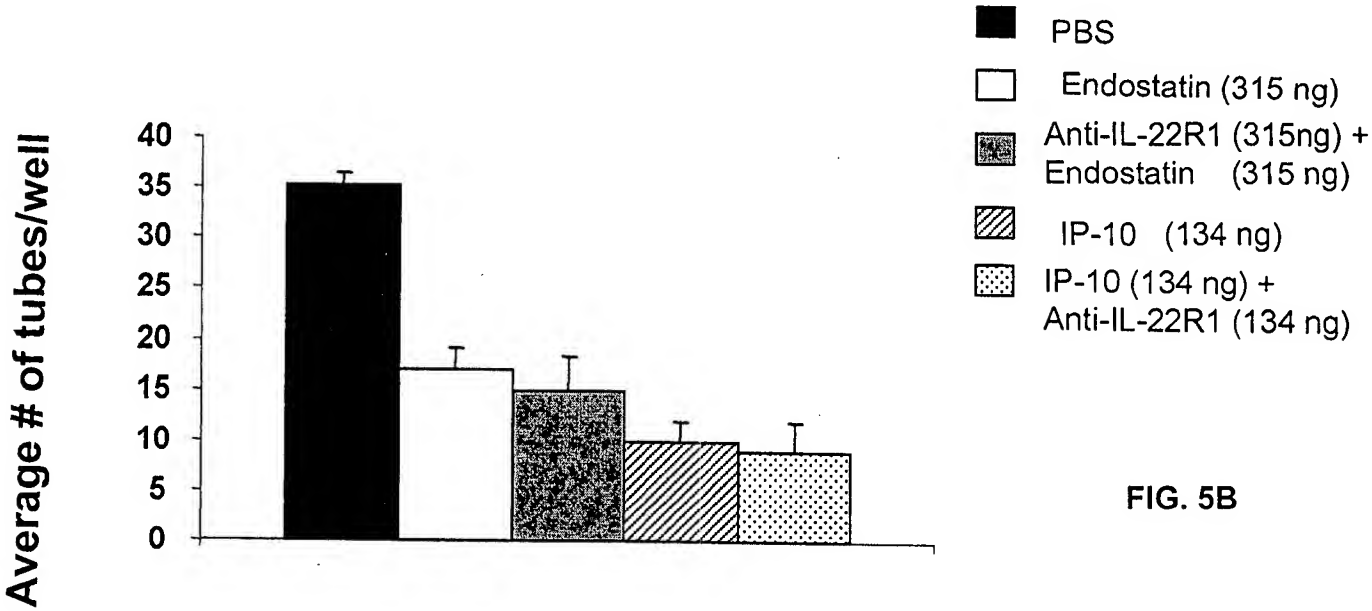

Average # of tubes/well
40
35
30
25
20
15
10
5
0
PBS
Endostatin (315 ng)
Anti-IL-22R1 (315ng) + Endostatin (315 ng)
IP-10 (134 ng)
IP-10 (134 ng) + Anti-IL-22R1 (134 ng)

FIG. 5B

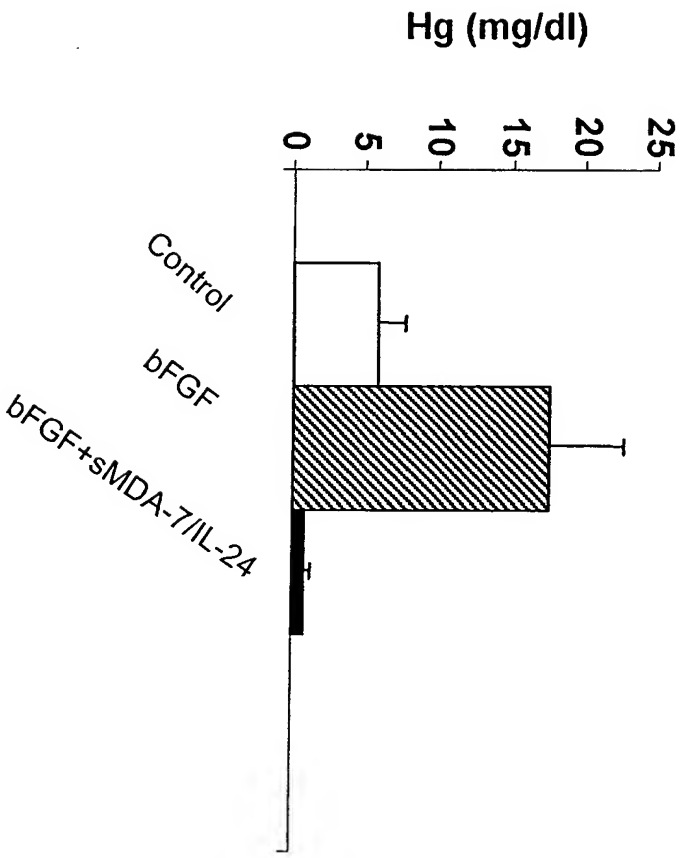


FIG. 6A

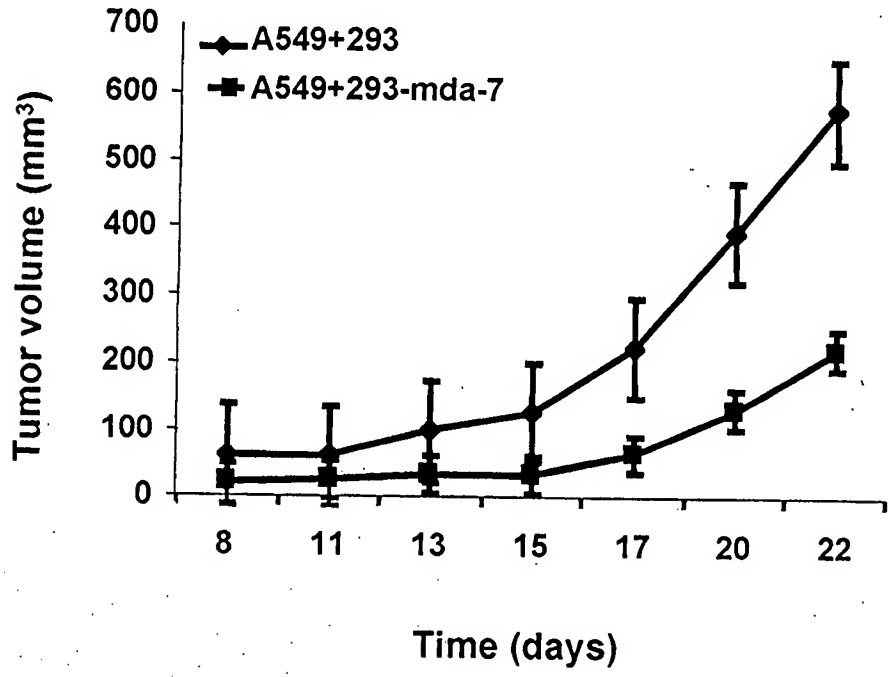

700
600
500
400
300
200
100
0
A549+293
A549+293-mda-7
Tumor volume (mm3)
8
11
13
15
17
20
22
Time (days)

FIG. 6B

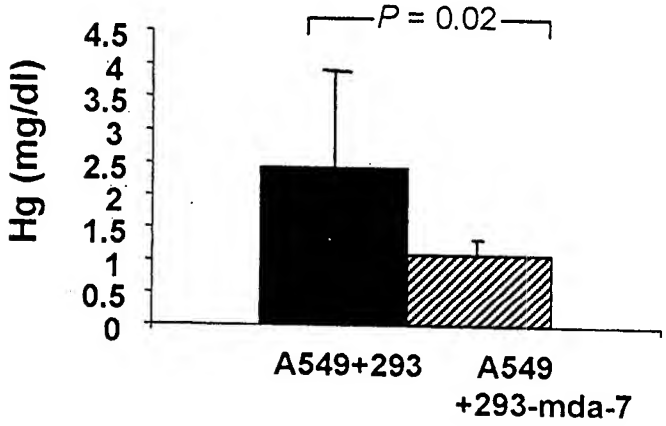

P = 0.02
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Hg (mg/dl)
A549+293
A549
+293-mda-7

FIG. 6C

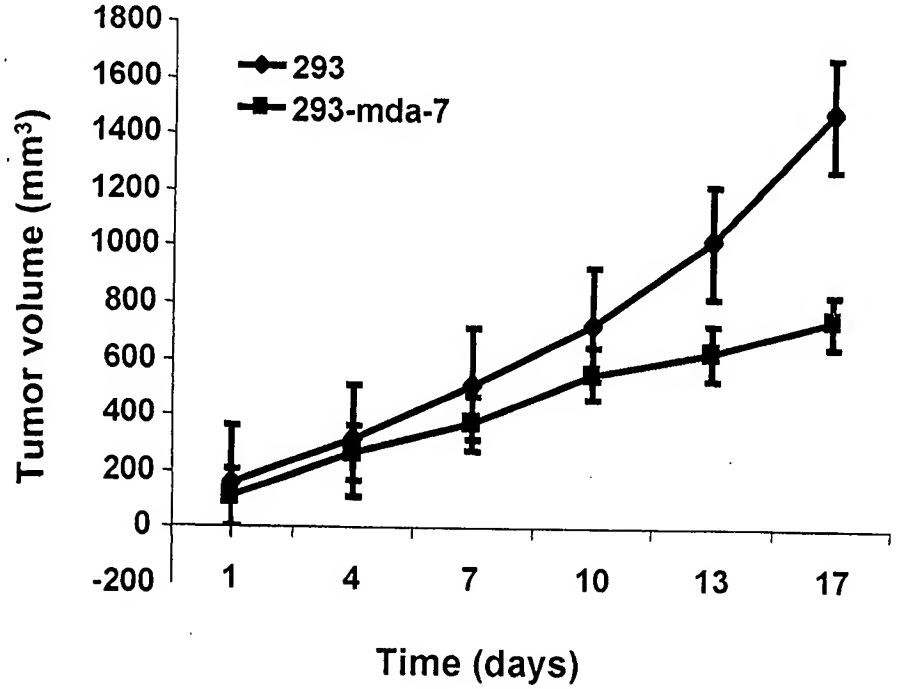
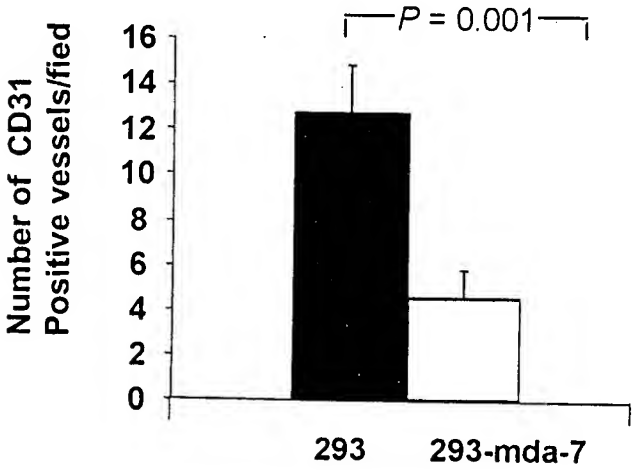

1800
1600
1400
1200
1000
800
600
400
200
0
-200
Tumor volume (mm3)
293
293-mda-7
1
4
7
10
13
17
Time (days)

FIG. 6D

FIG. 6E

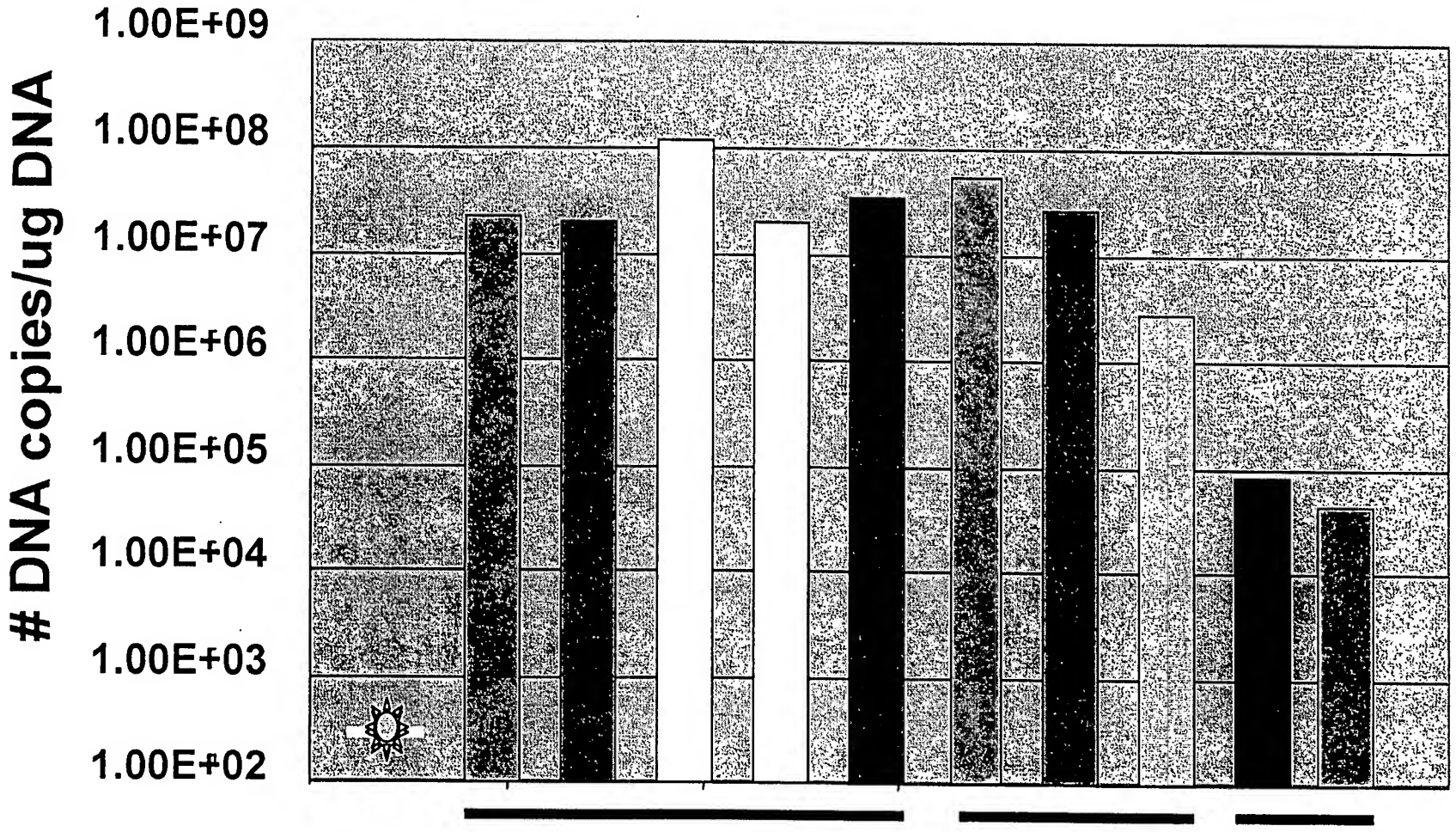

P = 0.001
16
14
12
10
8
6
4
2
0
Number of CD31 Positive vessels/fied
293
293-mda-7

Study design

FIG. 7

Cohort #	# of patients	Viral dose (particles)	biopsy time (post inj.)
1	1	$2x10^{10}$	24 hrs
2	1	$2x10^{11}$	24 hrs
3	3	$2x10^{12}$	24 hrs
4	3	$2x10^{12}$	48 hrs
5	3	$2x10^{12}$	72/96 hrs
6	3	$2x10^{12}$ (divided doses)	48 hrs
7	5	$2x10^{12}$	Core bx @30 days
8	5	$2x10^{12}$ (2x/wk x 3 wks)	Core bx @ 30 days

FIG. 8



☼: Average pre-treat signal is 4.4E+02, n=8

(Pre-treat MDA-7 IHC – all negative)

Pt	Time (hr)	MDA-7 ctr	MDA-7 periph	TUNEL ctr	TUNEL periph
1	24	20%	0 %	20 %	0 %
2	24	30 %	5 %	70 %	10 %
3	24	75 %	40 %	50 %	30 %
4	24	35 %	5 %	n.d.	n.d.
5	24	50 %	25 %	25 %	17 %
6	48	>60 %	20 %	40 %	17 %
7	48	60 %	5 %	70 %	10 %
8	48	20 %	0 %	5 %	0 %
9	96	50 %	25 %	80 %	25 %
10	96	90 %	0 %	35 %	0 %

FIG. 9 MDA-7/ TUNEL correlation $p < 0.01$

Kinetics of Serum Cytokine Response to INGN 241

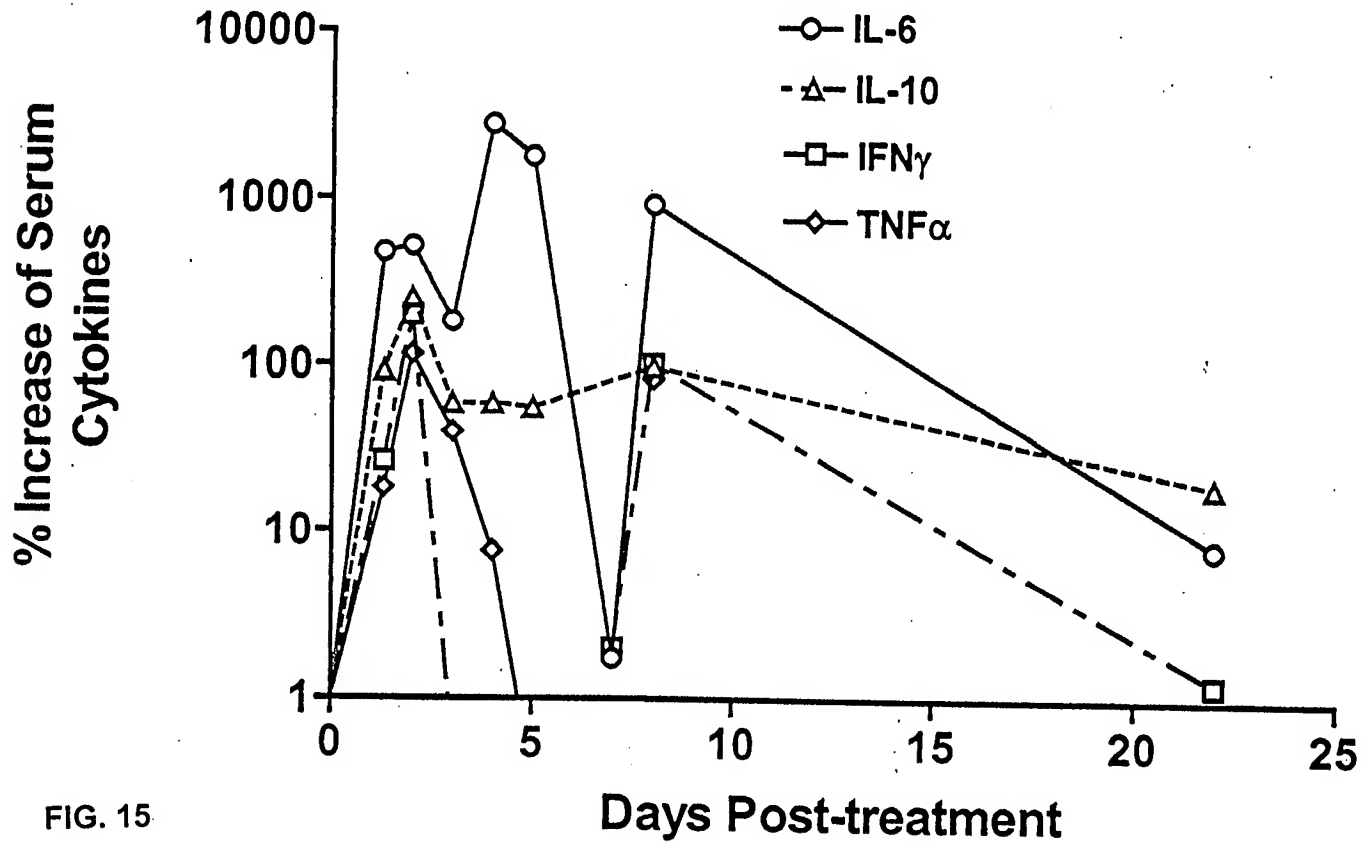


FIG. 15

FIG. 10

Serum Cytokine Response to Intratumoral INGN 241 Treatment.

Cohort (dose)	No. pts tested	No. positive (mean % peak increase) IL-6	IL-10	IFNγ	TNFα	GM-CSF
1 ($2x10^{10}$)	1	1 (298%)	1 (291%)	1 (>1,000%)	0	1 (150%)
2 ($2x10^{11}$)	1	1 (143%)	1 (599%)	1 (281%)	1 (864%)	0
3 ($2x10^{12}$)	3	1 (>1,000%)	1 (134%)	1 (317%)	2 (345%)	1 (100%)
4 ($2x10^{12}$)	3	3 (>1,000%)	3 (221%)	1 (173%)	2 (71%)	1 (120%)
5 ($2x10^{12}$)	3	3 (640%)	3 (400%)	1 (317%)	2 (156 %)	0
7 ($2x10^{12}$)	7	5 (604%)	6 (387%)	3 (860%)	3 (255%)	0
Total	18	14	15	8	10	3

FIG. 11

Level of Increased CD8+ T cell Frequency in Pts who Received Intratumoral INGN 241.

Cohort (dose)	No. pts tested	No. with increased CD8+ T cells	Mean % CD3+CD8+ T cells[1]		
			Pre-treatment	Post-treatment @	Day Post-treat.
1 ($2x10^{10}$)	1	0	29 %	27%	
2 ($2x10^{11}$)	1	1	32 %	44%	Day 15
3 ($2x10^{12}$)	3	3	33%	59%	Day 15
4 ($2x10^{12}$)	3	1	35%	44%	Day 30
5 ($2x10^{12}$)	3	1	22%	29%	Day 15
7 ($2x10^{12}$)	7	2	30%	40%	Days 15-30
Total	18	8	31%	44%	Day 15

FIG. 12

Increase in Peripheral Blood CD8+ T Cells Following intratumoral INGN 241 Injection

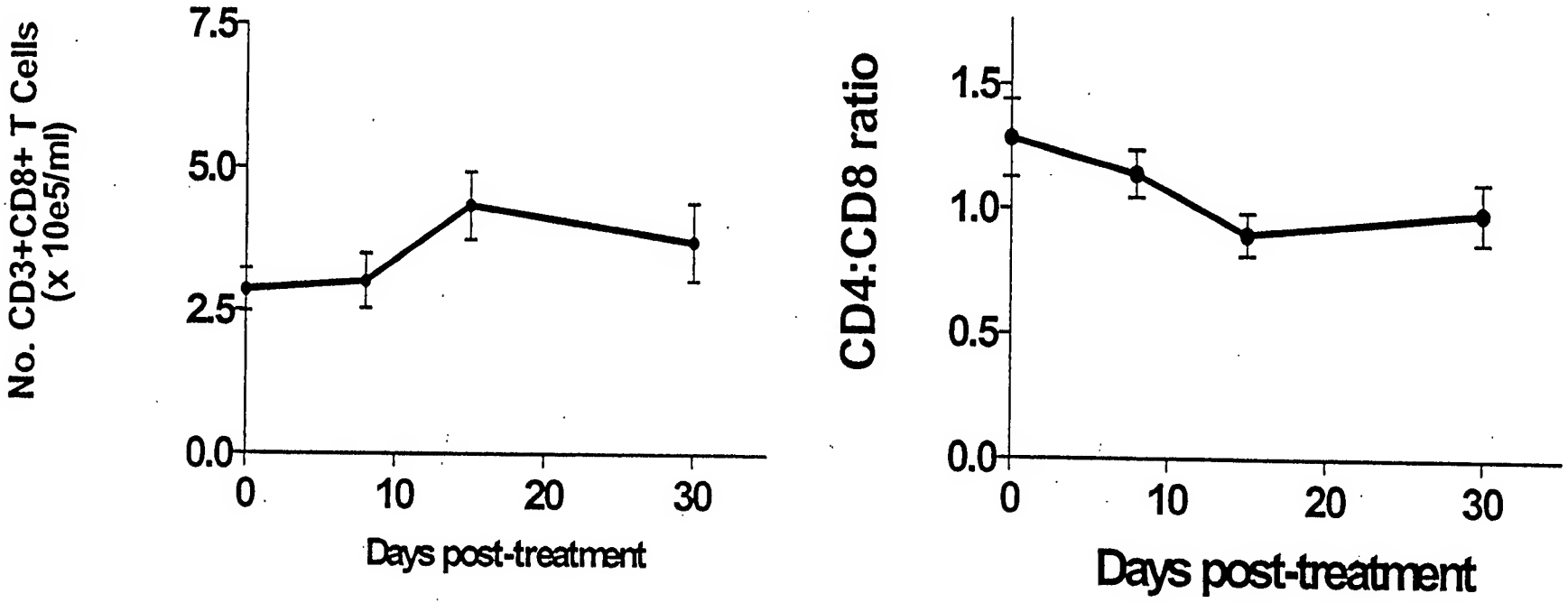


FIG. 13

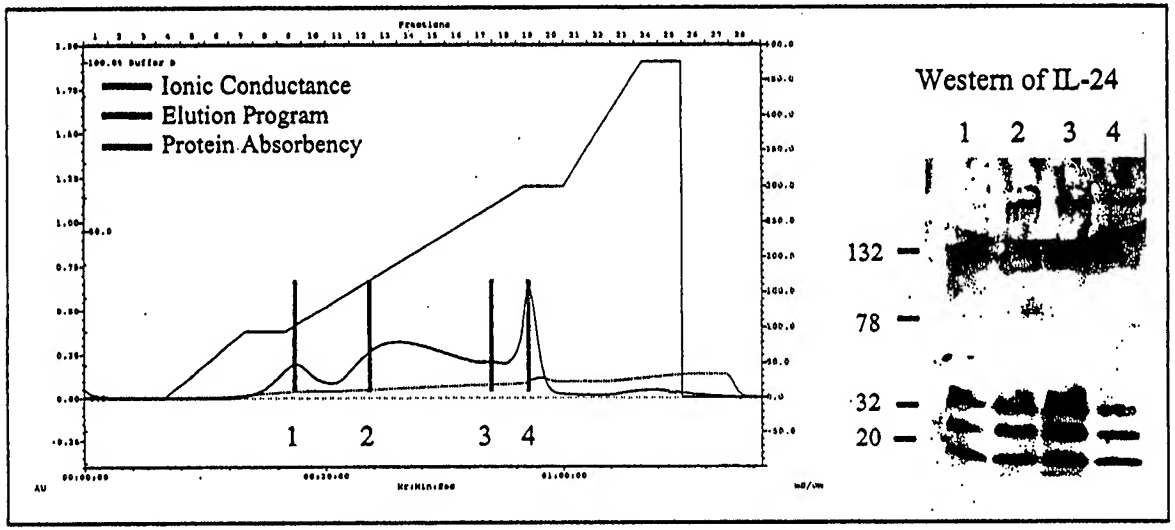

Ionic Conductance
Elution Program
Protein Absorbency
1
2
3
4
Western of IL-24
1
2
3
4
132
78
32
20

FIG. 14

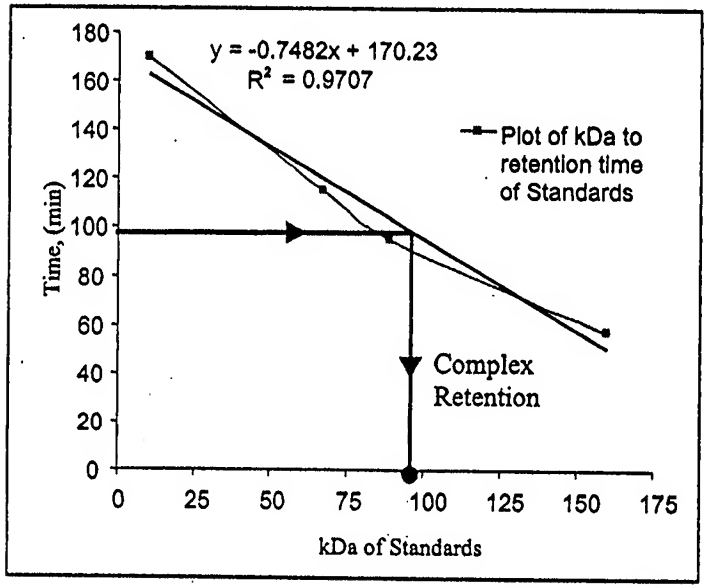

y = -0.7482x + 170.23
R² = 0.9707
Plot of kDa to retention time of Standards
Complex Retention
Time, (min)
kDa of Standards
180
160
140
120
100
80
60
40
20
0
0
25
50
75
100
125
150
175

FIG. 15

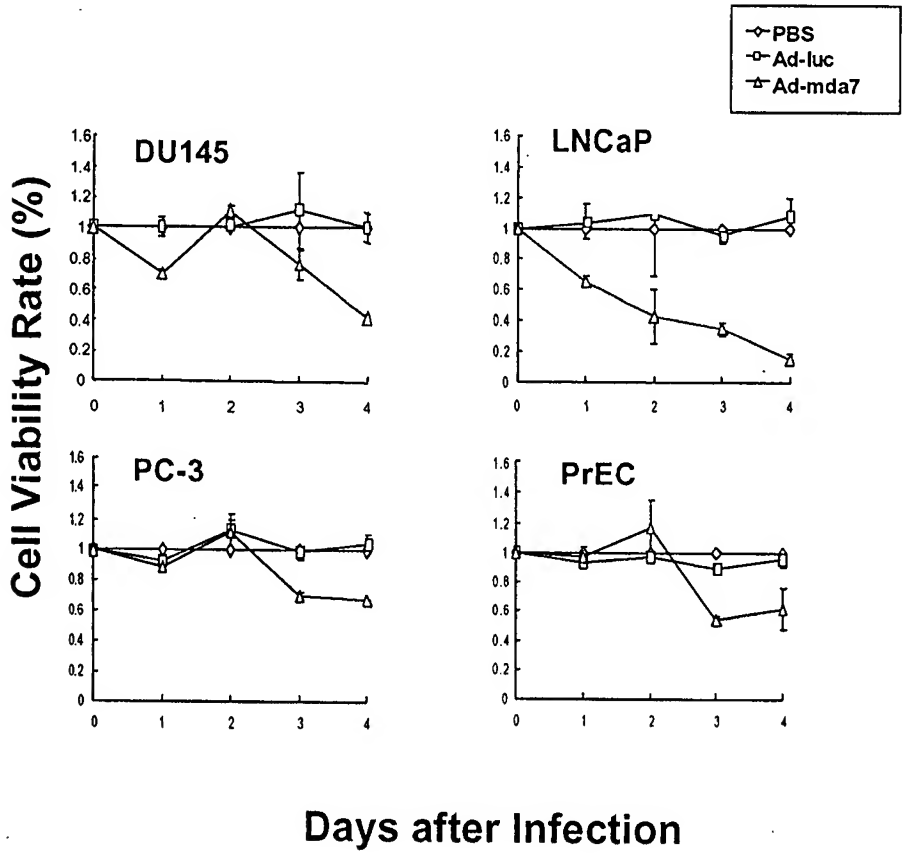

PBS
Ad-luc
Ad-mda7
DU145
LNCaP
PC-3
PrEC
Cell Viability Rate (%)
Days after Infection

FIG. 16

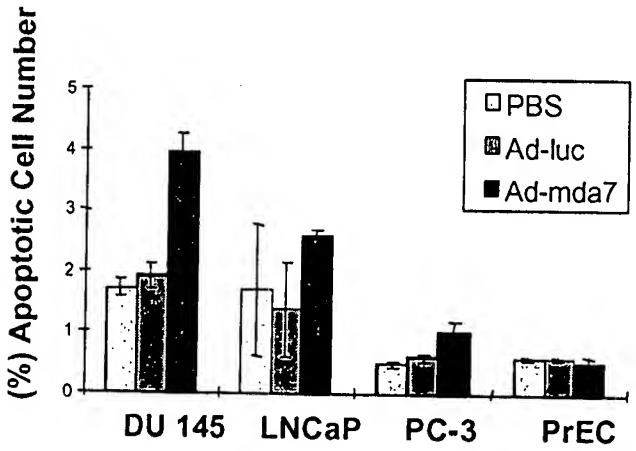

(%) Apoptotic Cell Number
5
4
3
2
1
0
PBS
Ad-luc
Ad-mda7
DU 145
LNCaP
PC-3
PrEC

FIG. 17

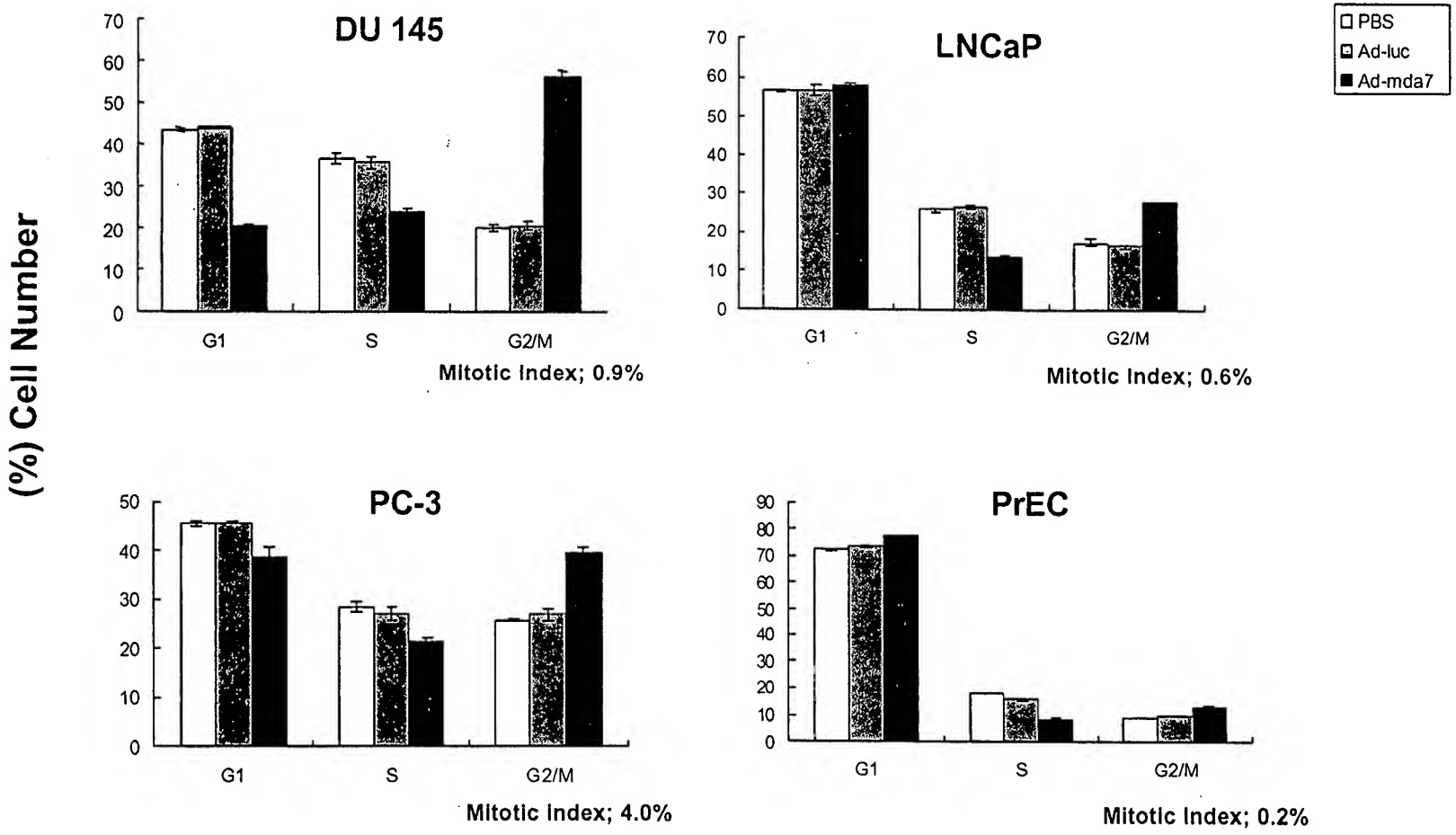

DU 145
LNCaP
PC-3
PrEC
PBS
Ad-luc
Ad-mda7
(%) Cell Number
G1
S
G2/M
Mitotic Index; 0.9%
Mitotic Index; 0.6%
Mitotic Index; 4.0%
Mitotic Index; 0.2%
Cell Cycle Phase

FIG. 18

FIG. 19A

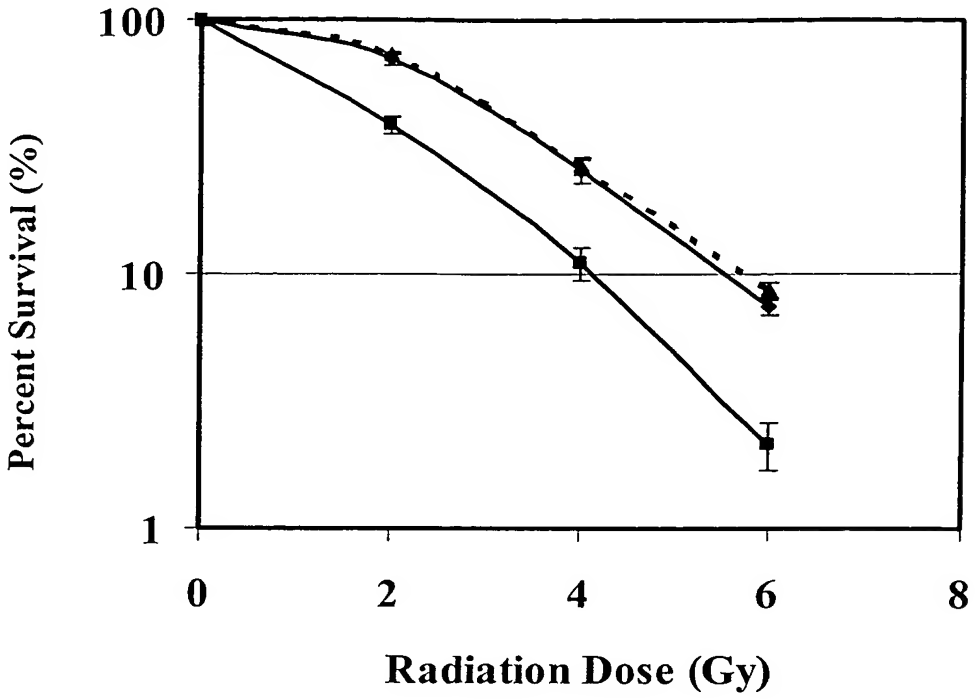
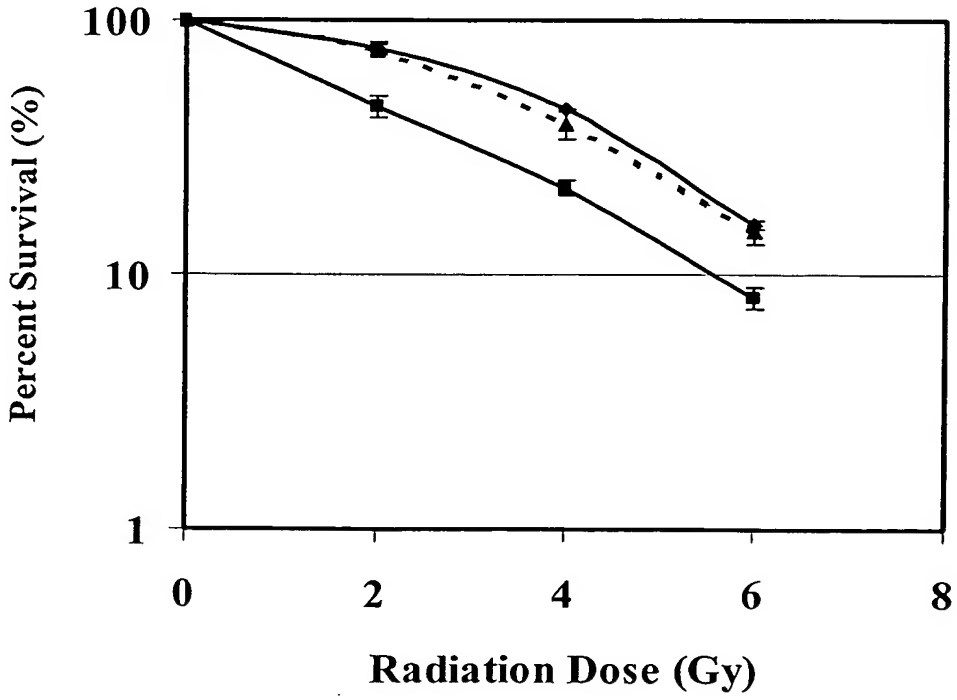


FIG. 19B



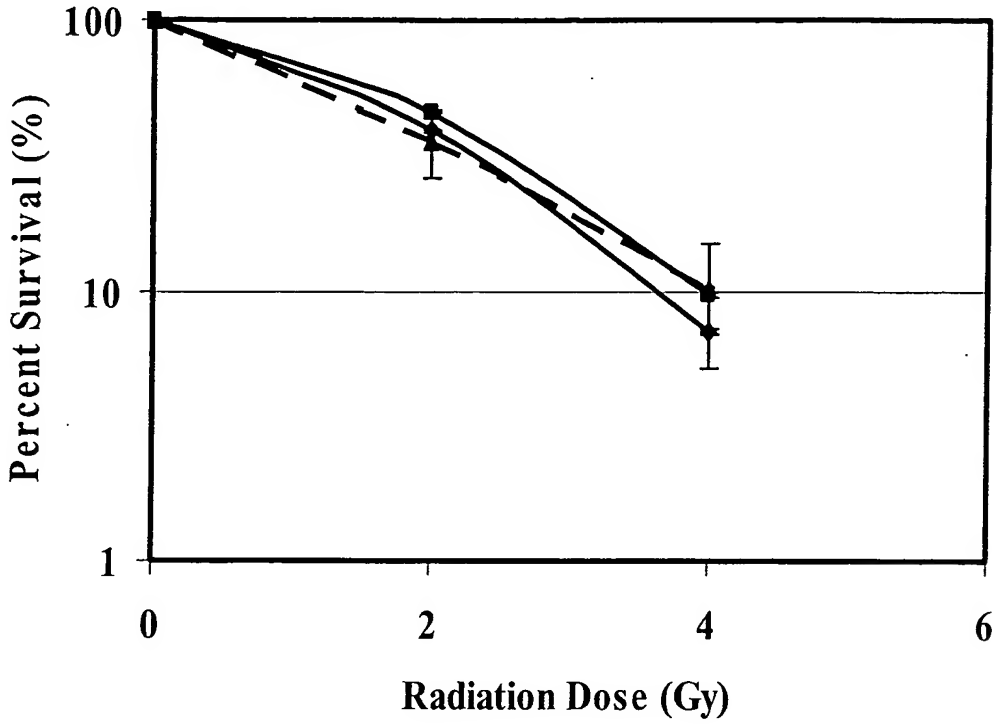


FIG. 19C

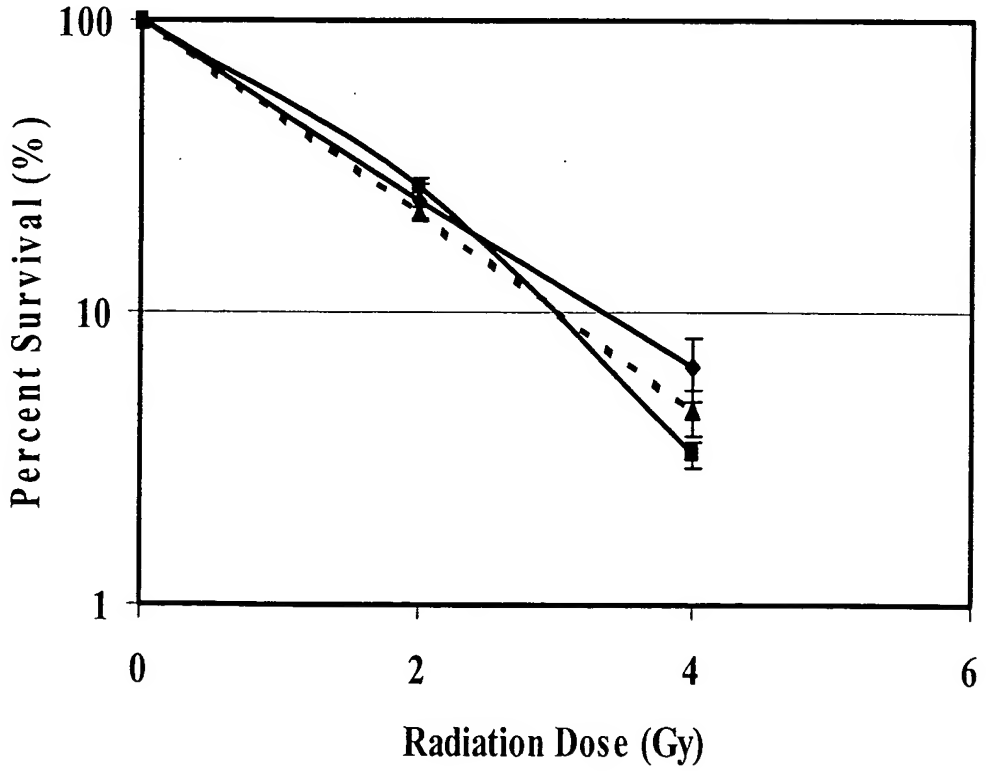


FIG. 19D

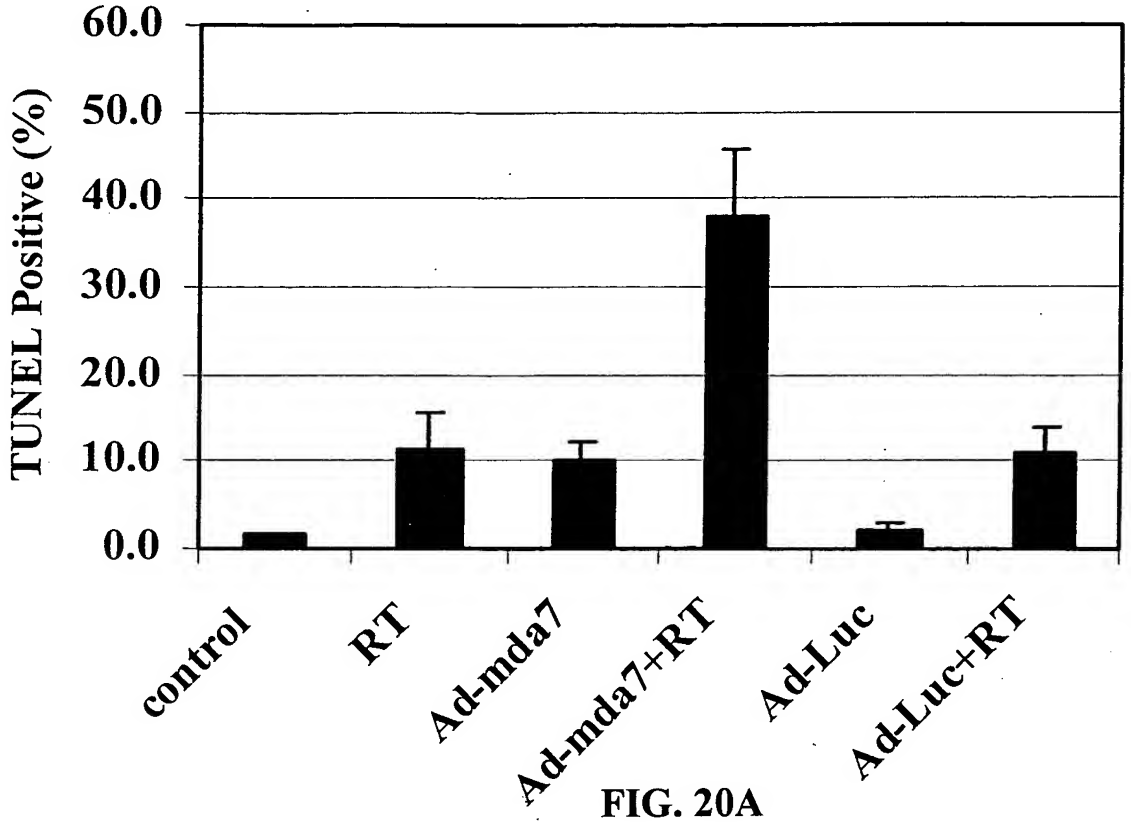


FIG. 20A

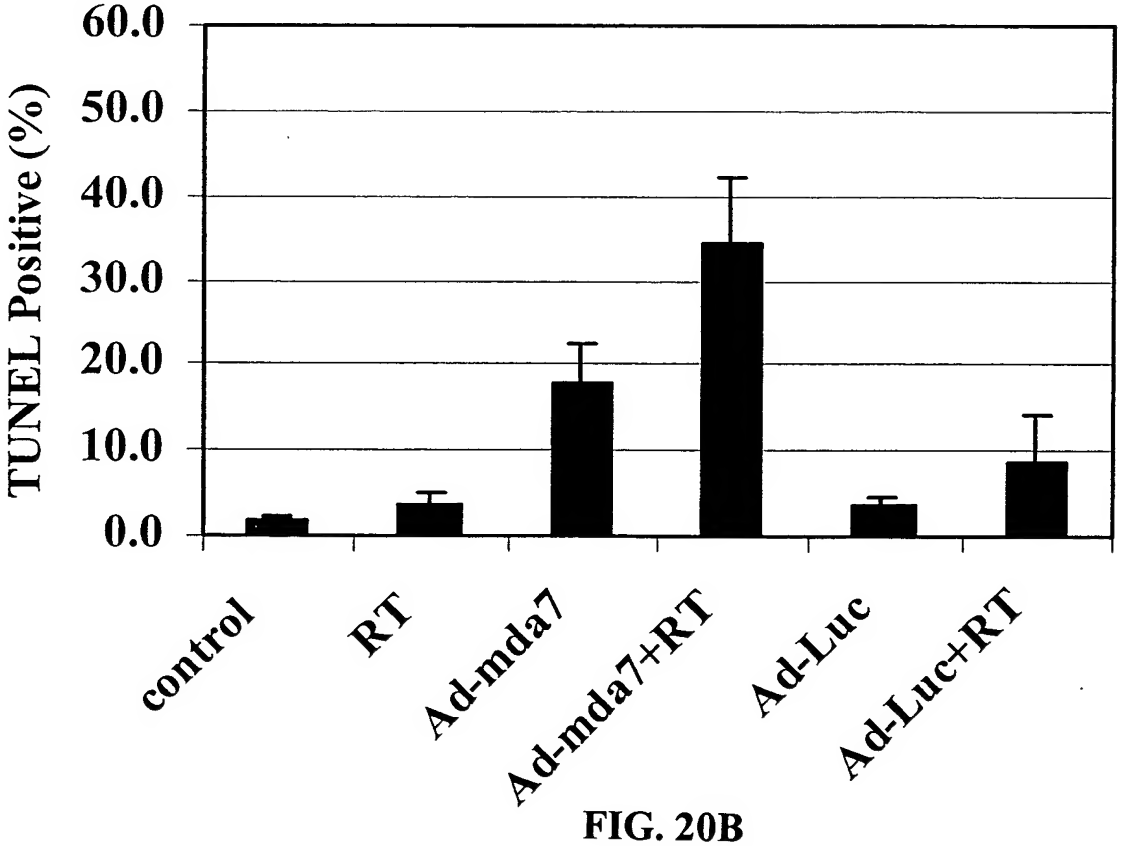


FIG. 20B

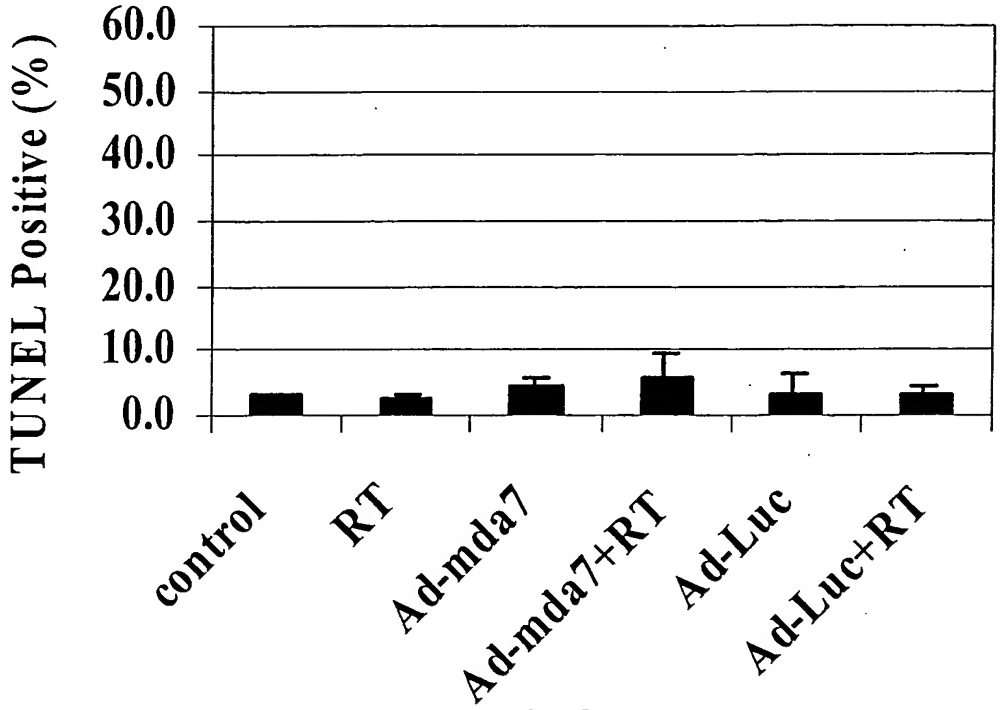


FIG. 20C

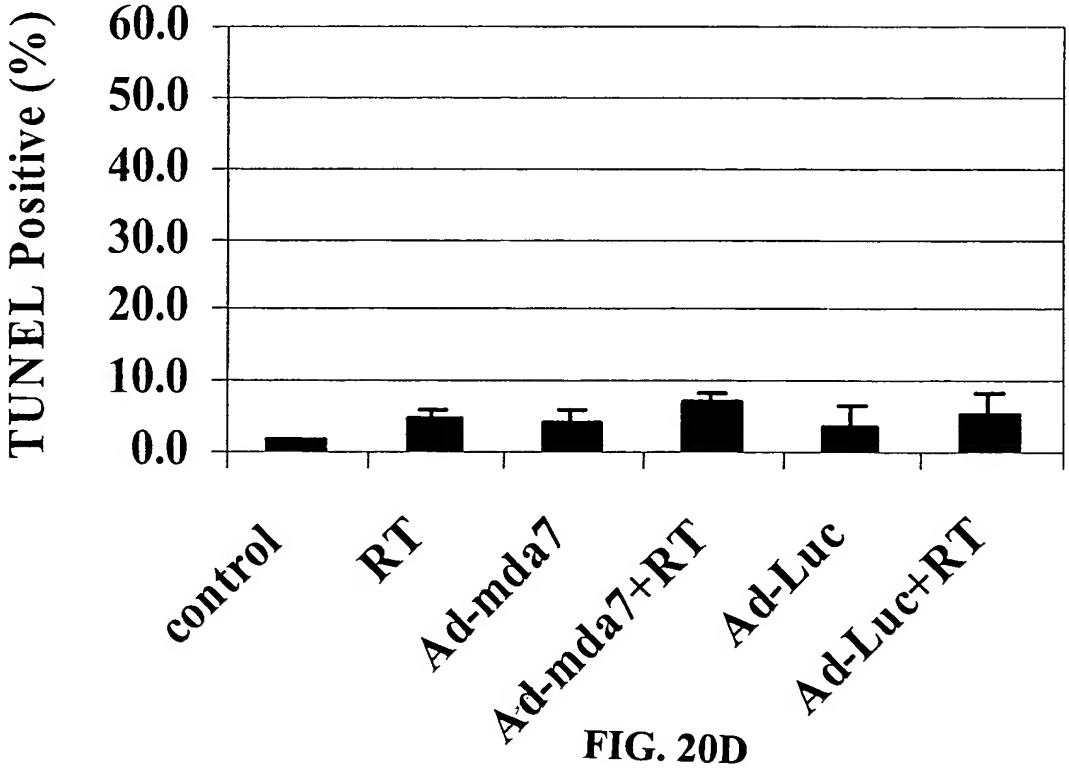
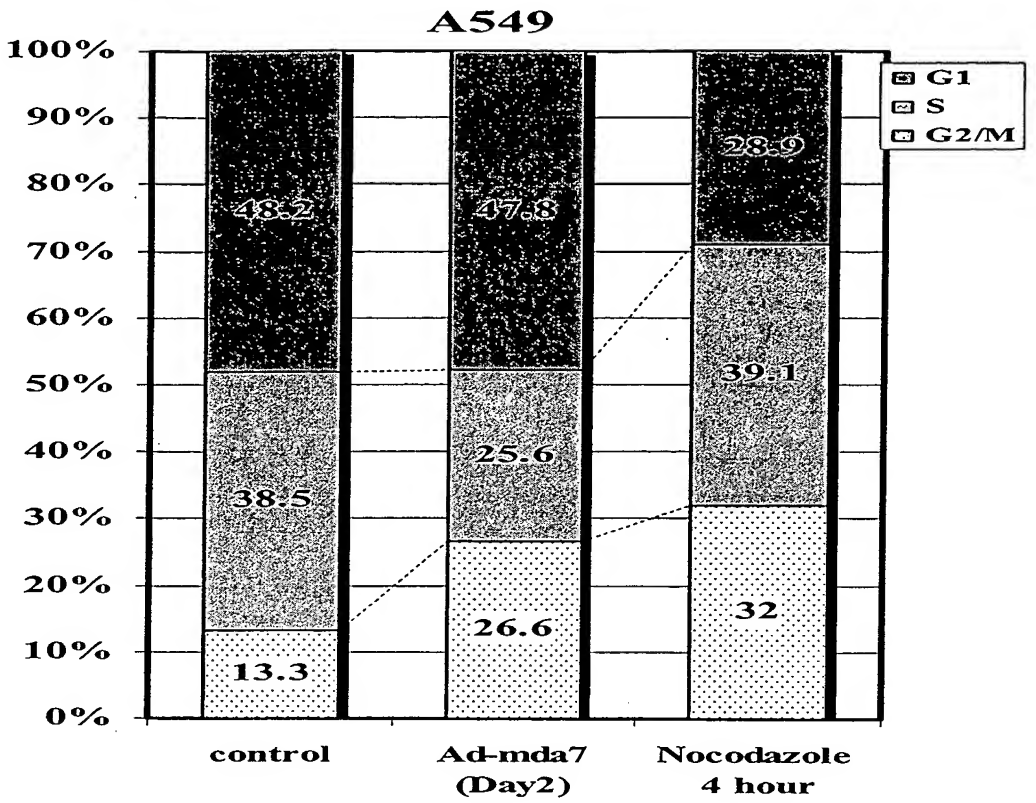


FIG. 20D


A549
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
48.2
38.5
13.3
47.8
25.6
26.6
28.9
39.1
32
G1
S
G2/M
control
Ad-mda7
(Day2)
Nocodazole
4 hour

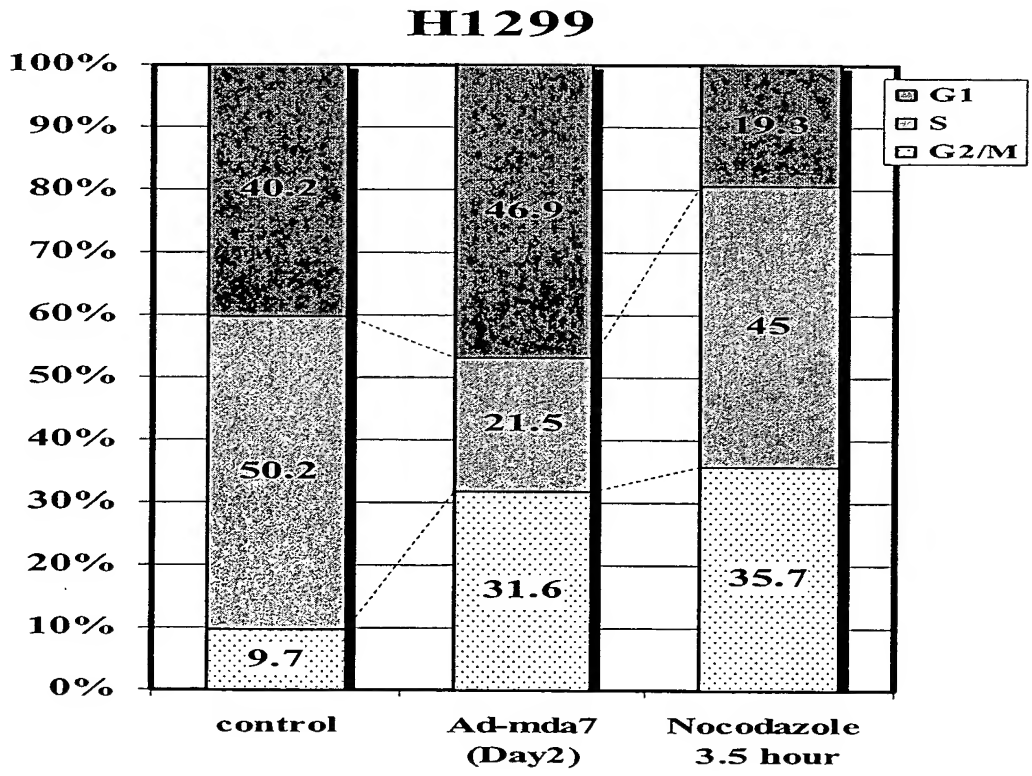
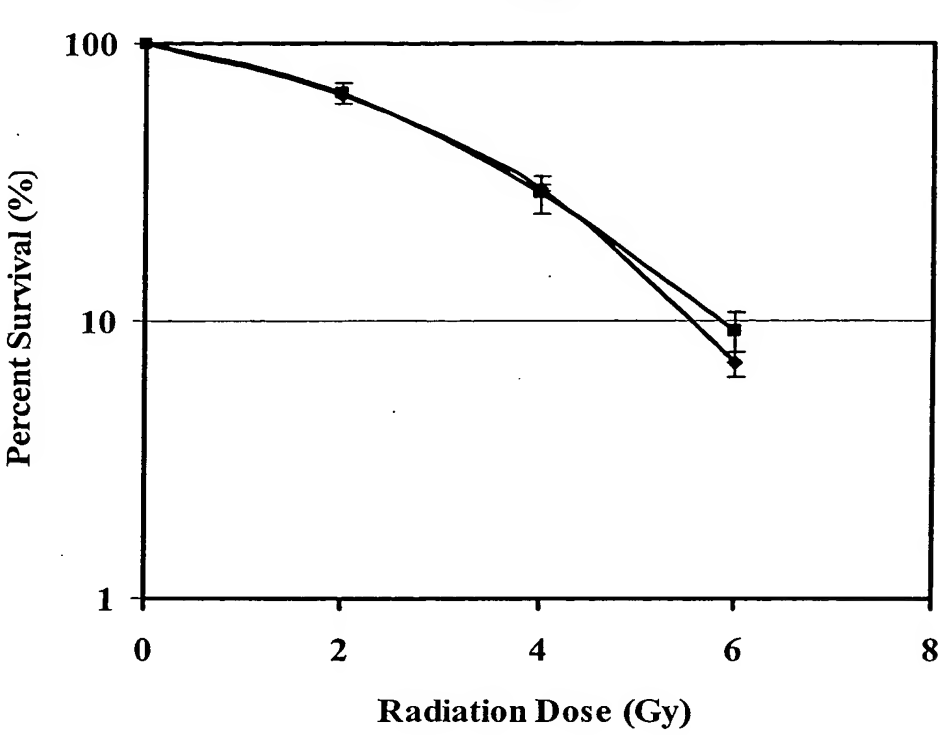

H1299
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
40.2
50.2
9.7
46.9
21.5
31.6
19.3
45
35.7
G1
S
G2/M
control
Ad-mda7
(Day2)
Nocodazole
3.5 hour

FIG. 21


A549
100
10
1
Percent Survival (%)
0
2
4
6
8
Radiation Dose (Gy)

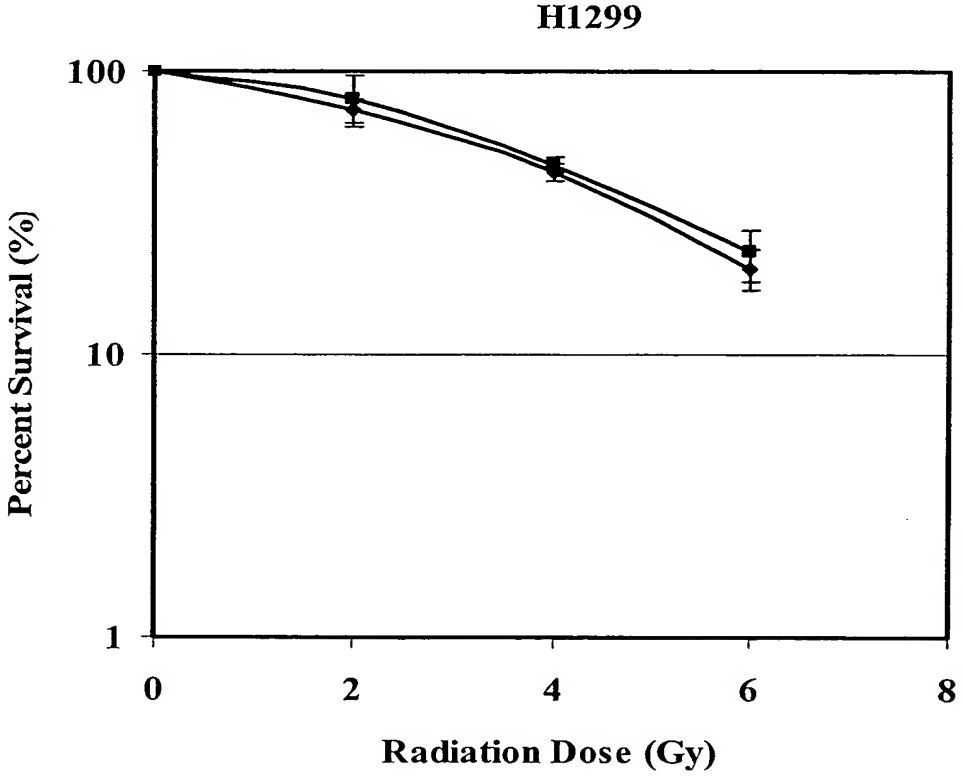
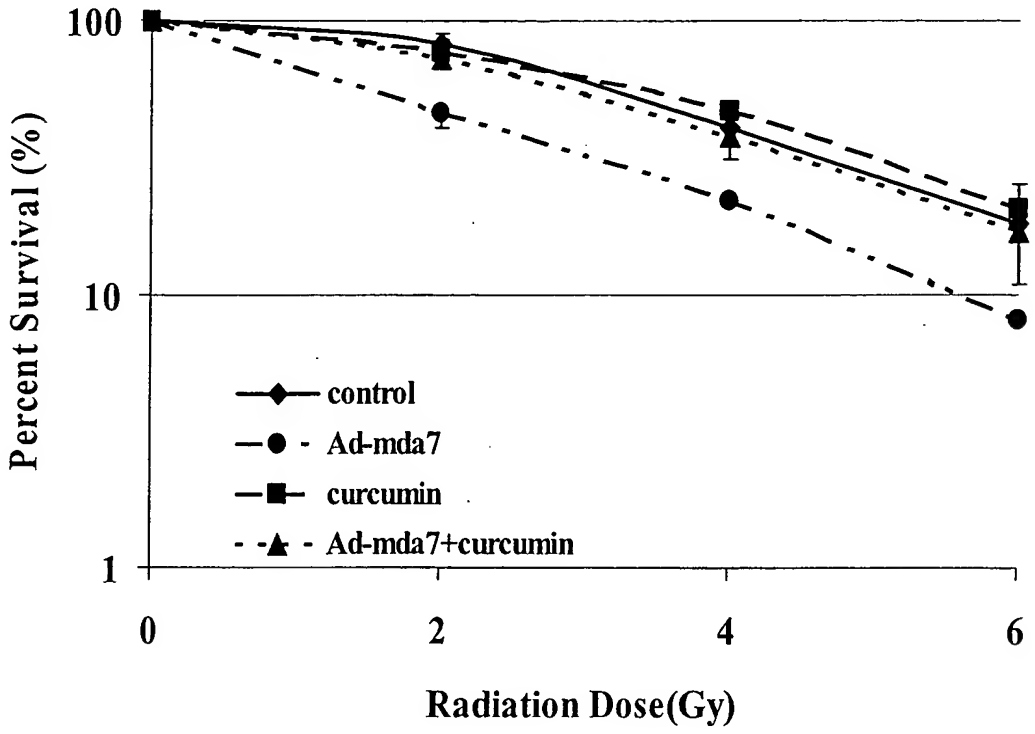

H1299
100
10
1
Percent Survival (%)
0
2
4
6
8
Radiation Dose (Gy)

FIG. 22

H1299



A549

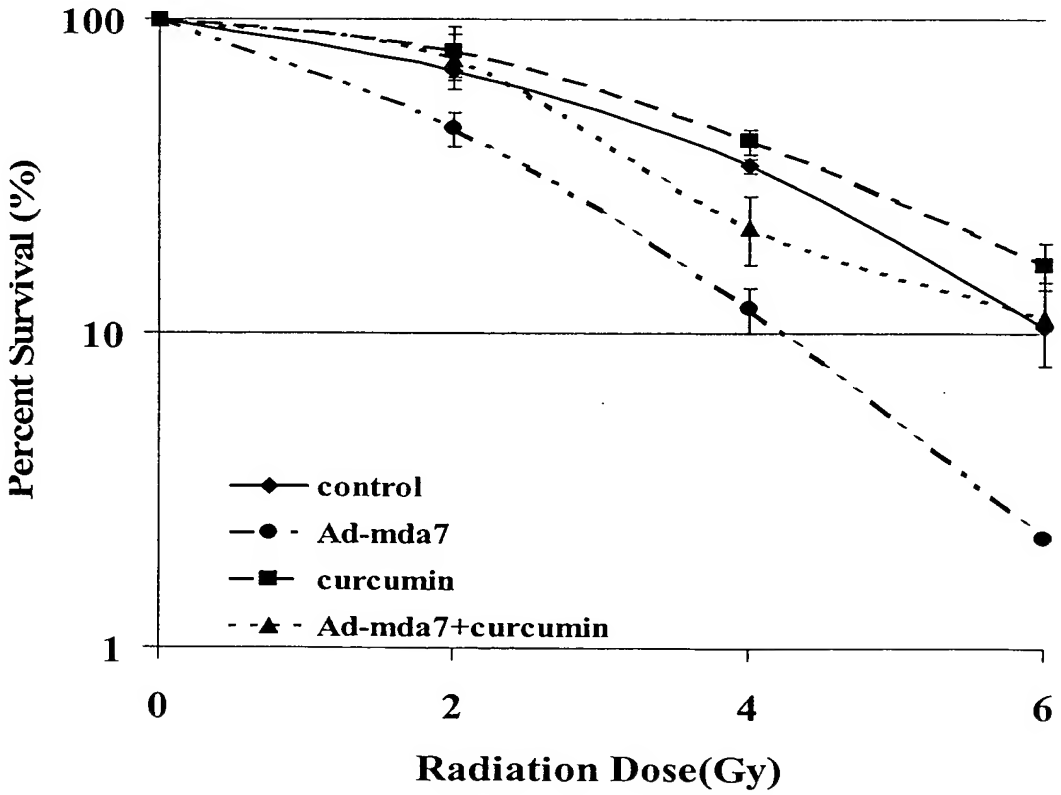


FIG. 23

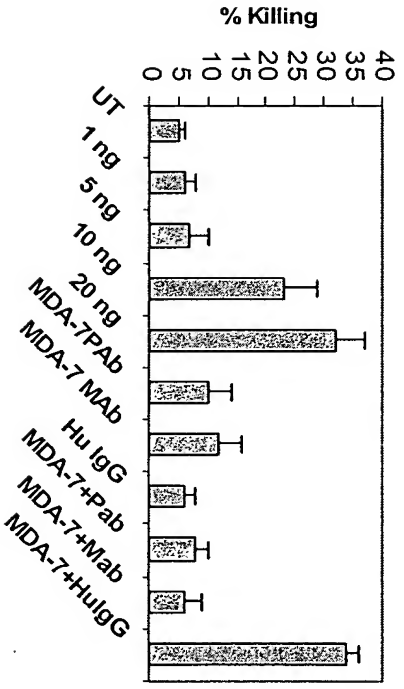
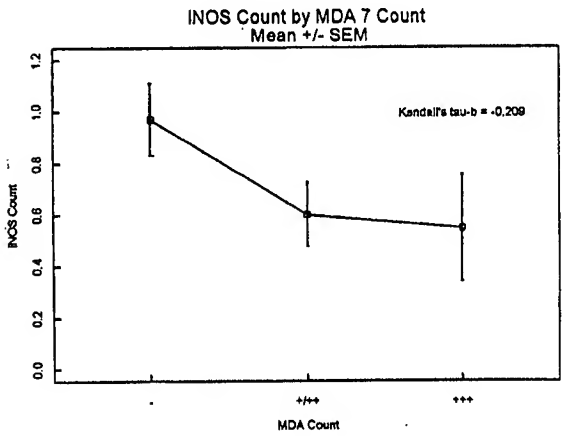

% Killing
0
5
10
15
20
25
30
35
40
UT
1 ng
5 ng
10 ng
20 ng
MDA-7PAb
MDA-7 MAb
Hu IgG
MDA-7+Pab
MDA-7+Mab
MDA-7+HulgG

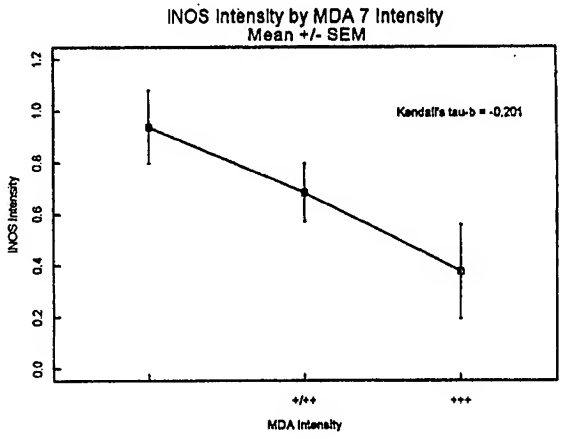
FIG. 24

A



MDA-7 count	Average iNOS count	SE	N
-	.97	.13	35
+/++	.60	.12	35
+++	.54	.21	11

B



MDA-7 count	Average iNOS count	SE	N
-	1.21	.16	32
+/++	.90	.14	41
+++	.50	.27	8

FIG. 25

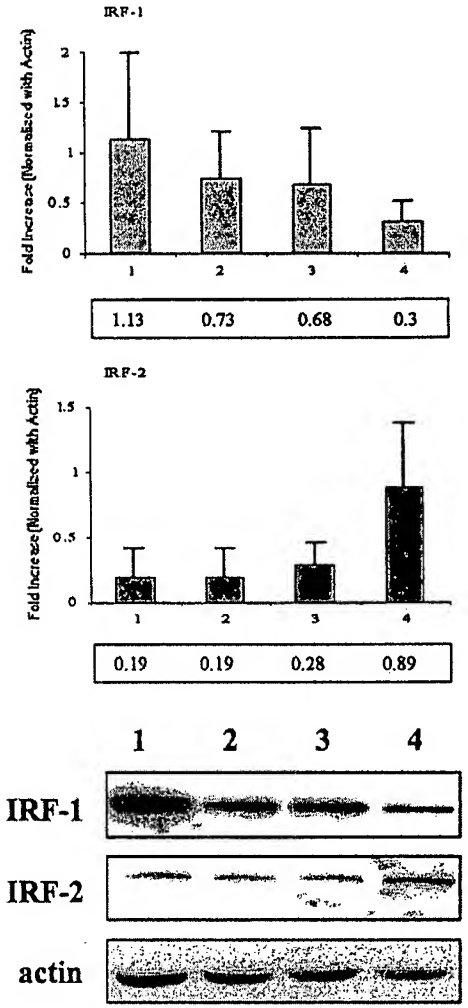

IRF-1
Fold Increase (Normalized with Actin)
2
1.5
1
0.5
0
1
2
3
4
1.13
0.73
0.68
0.3
IRF-2
Fold Increase (Normalized with Actin)
1.5
1
0.5
0
1
2
3
4
0.19
0.19
0.28
0.89
1
2
3
4
IRF-1
IRF-2
actin

FIG. 26

FIG. 27

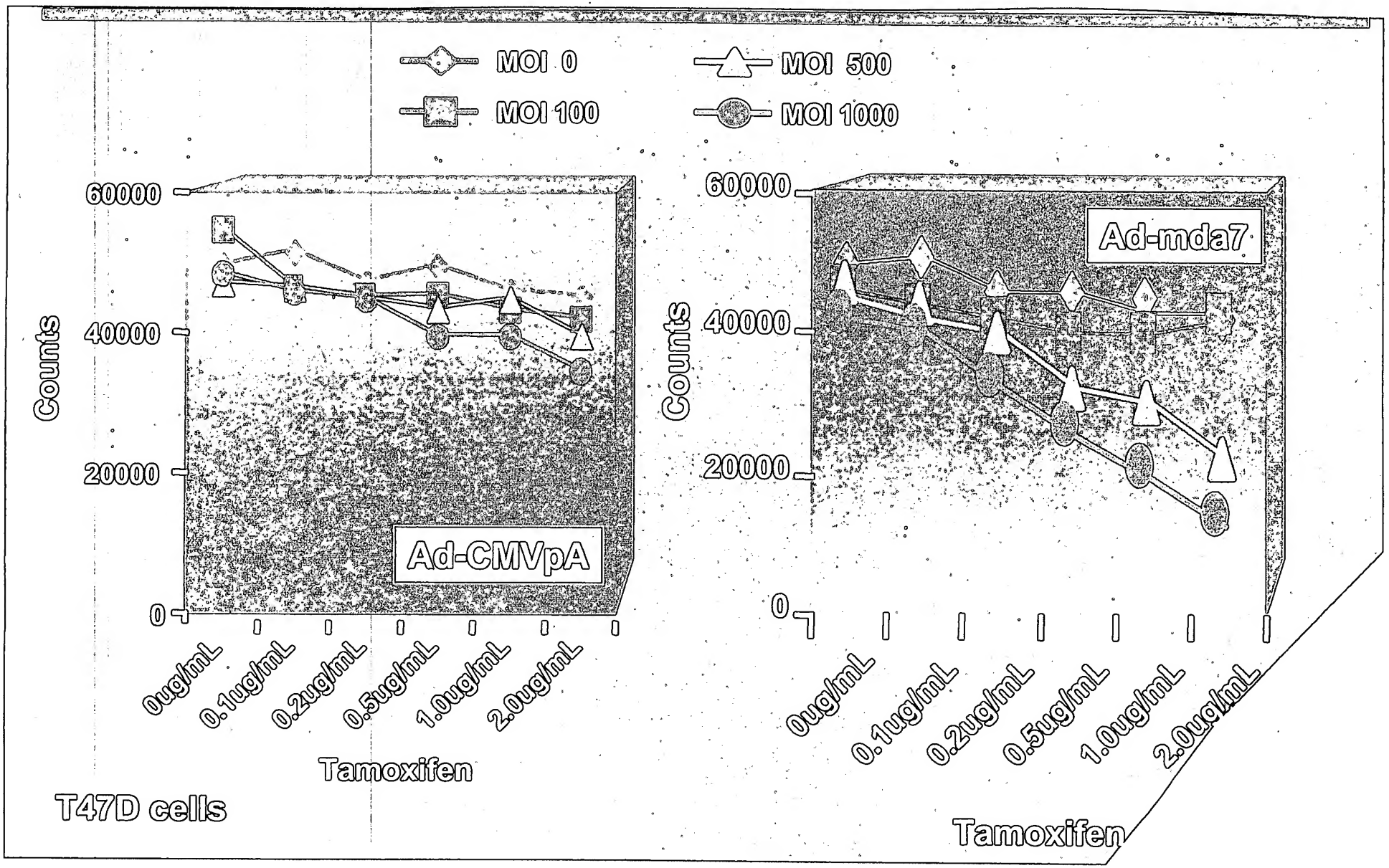

MOI 0
MOI 100
MOI 500
MOI 1000
60000
40000
20000
0
Counts
Ad-CMVpA
Ad-mda7
0ug/mL
0.1ug/mL
0.2ug/mL
0.5ug/mL
1.0ug/mL
2.0ug/mL
Tamoxifen
T47D cells

FIG. 28

	IL-6	IFN-g	IL-10	GM-CSF	s.Fas	IL-1b	TNF-a	pSTAT3
Ad-mda7	++	++	decrease	+/-	++	-	-	++
MDA-7	+	+++	decrease	n.d.	n.d.	n.d.	n.d.	++

+ -> +++: increased cytokine secretion compared to Ad-luc control.
- : no change; n.d.: not done.
Cytokine levels were evaluated using ELISA from cultured cell supernatants taken 24-72 hr post treatment.
pSTAT3 results were analyzed 4hr after addition of MDA-7 protein and 24 hr after Ad-mda7 treatment using IHC.

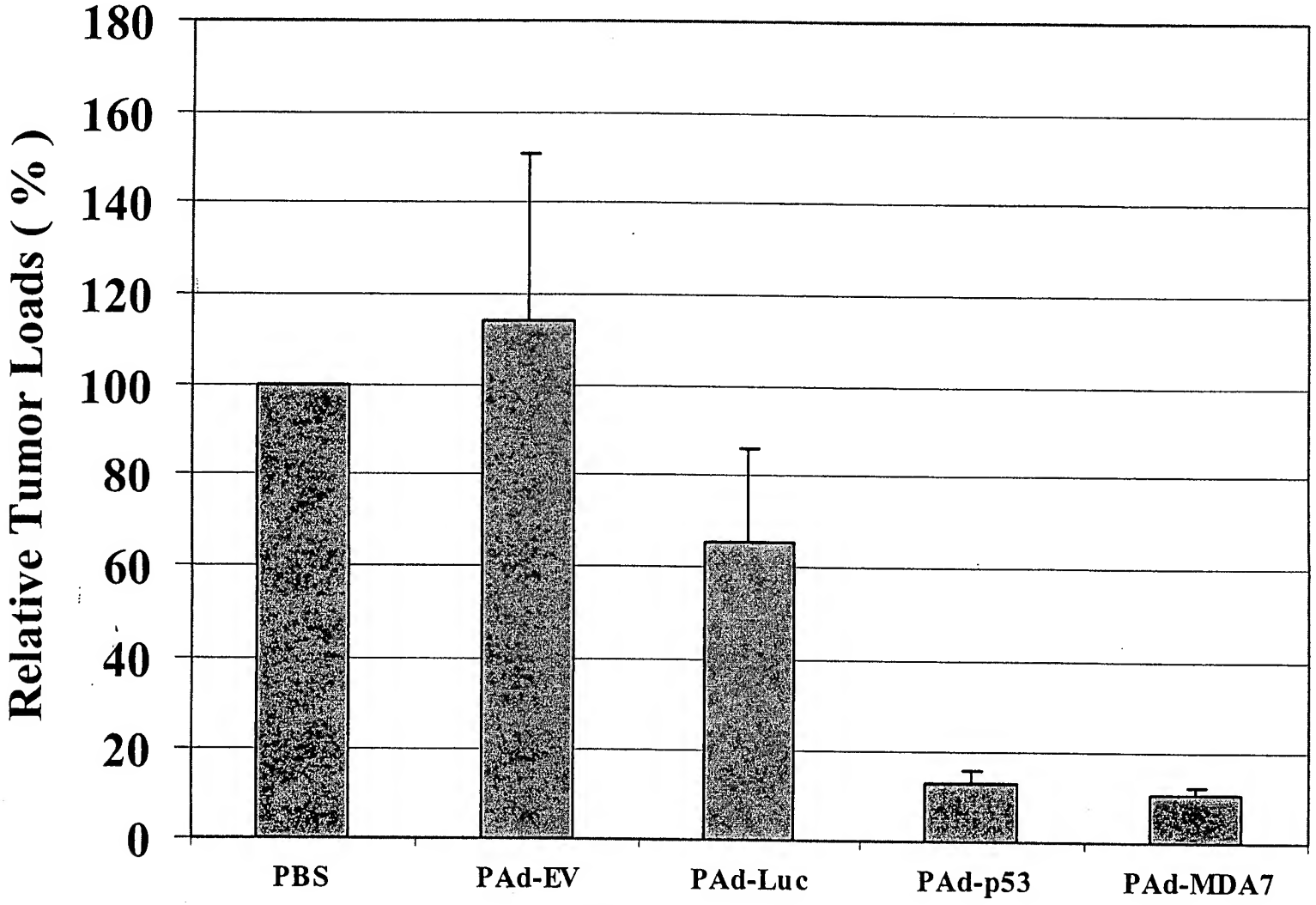

Effect of Ad-mda7on A549 Lung Metastasis
Relative Tumor Loads (%)
180
160
140
120
100
80
60
40
20
0
PBS
PAd-EV
PAd-Luc
PAd-p53
PAd-MDA7

FIG. 29

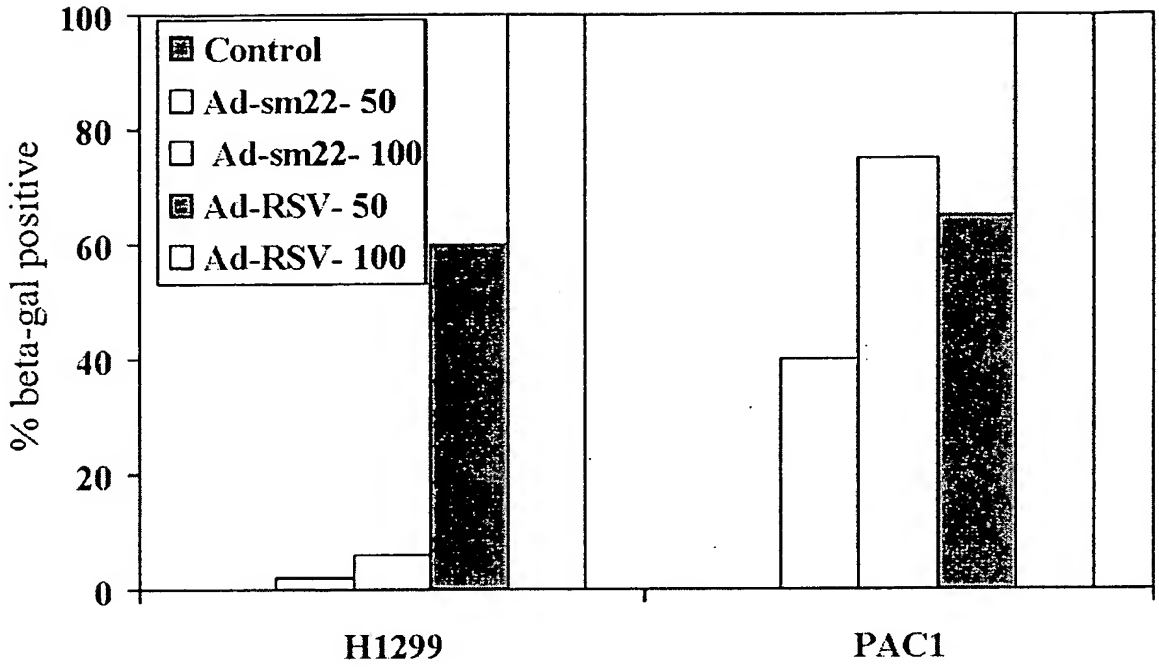

100
80
60
40
20
0
% beta-gal positive
Control
Ad-sm22- 50
Ad-sm22- 100
Ad-RSV- 50
Ad-RSV- 100
H1299
PAC1

FIG. 30

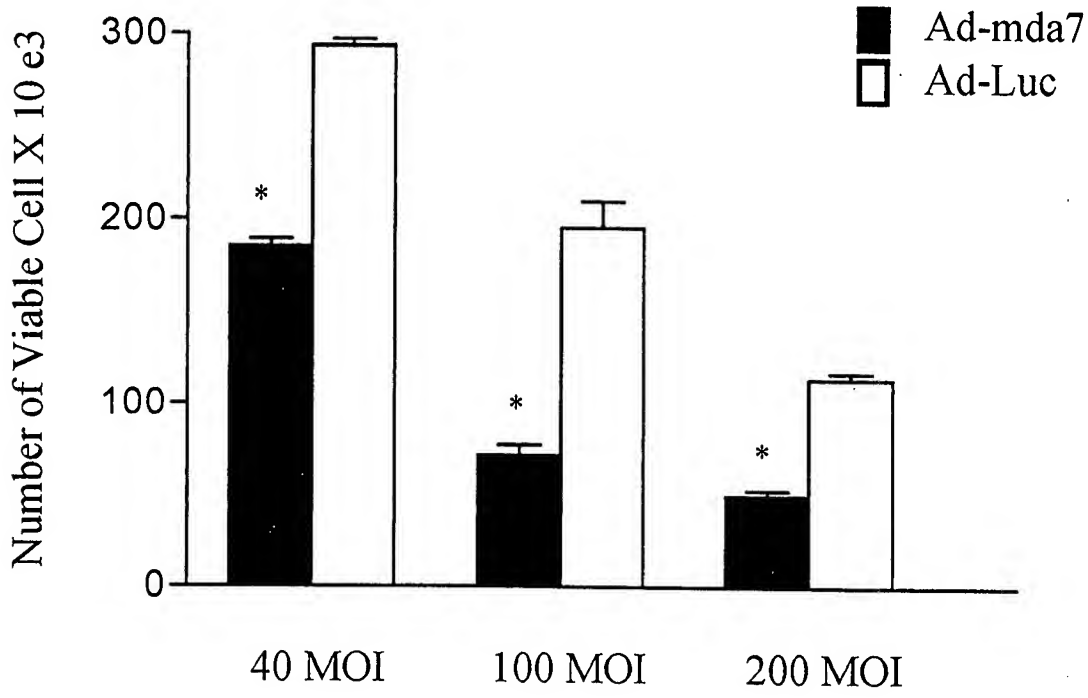

Number of Viable Cell X 10 e3
300
200
100
0
Ad-mda7
Ad-Luc
*
*
*
40 MOI
100 MOI
200 MOI

FIG. 31

A

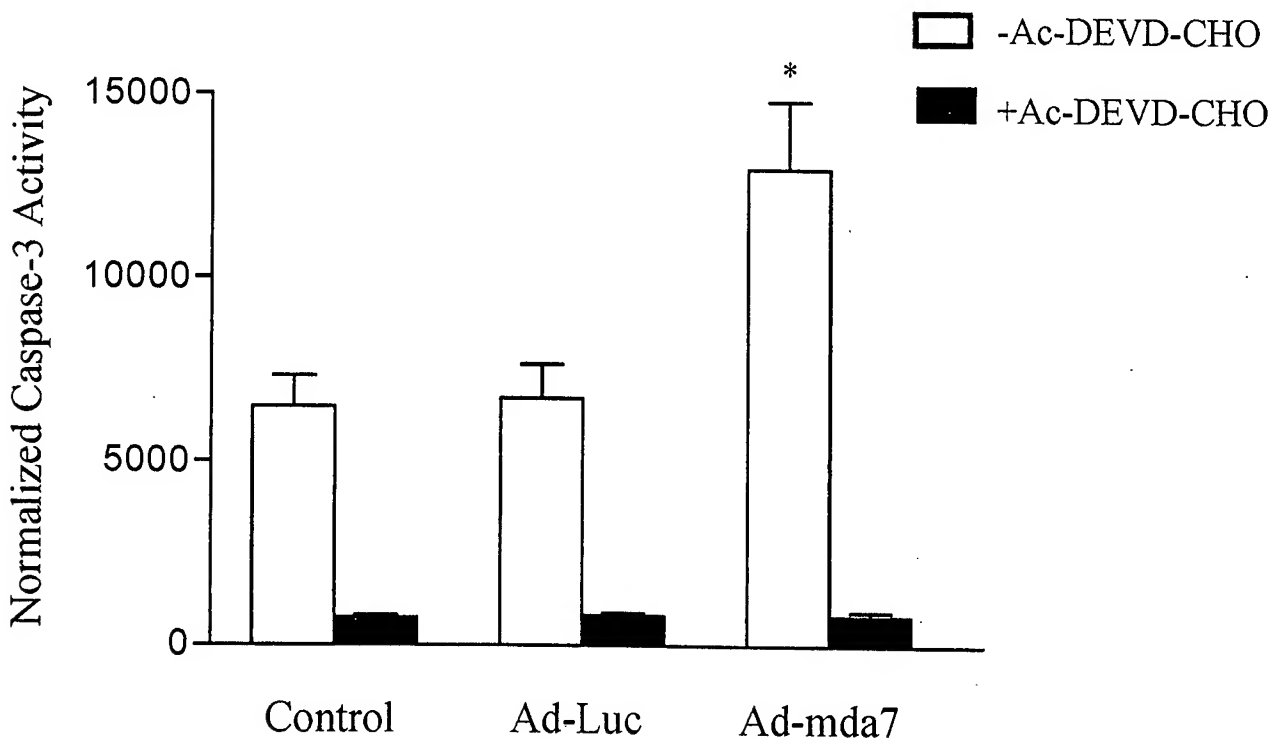

-Ac-DEVD-CHO
+Ac-DEVD-CHO
Normalized Caspase-3 Activity
15000
10000
5000
0
*
Control
Ad-Luc
Ad-mda7

FIG. 32A

B

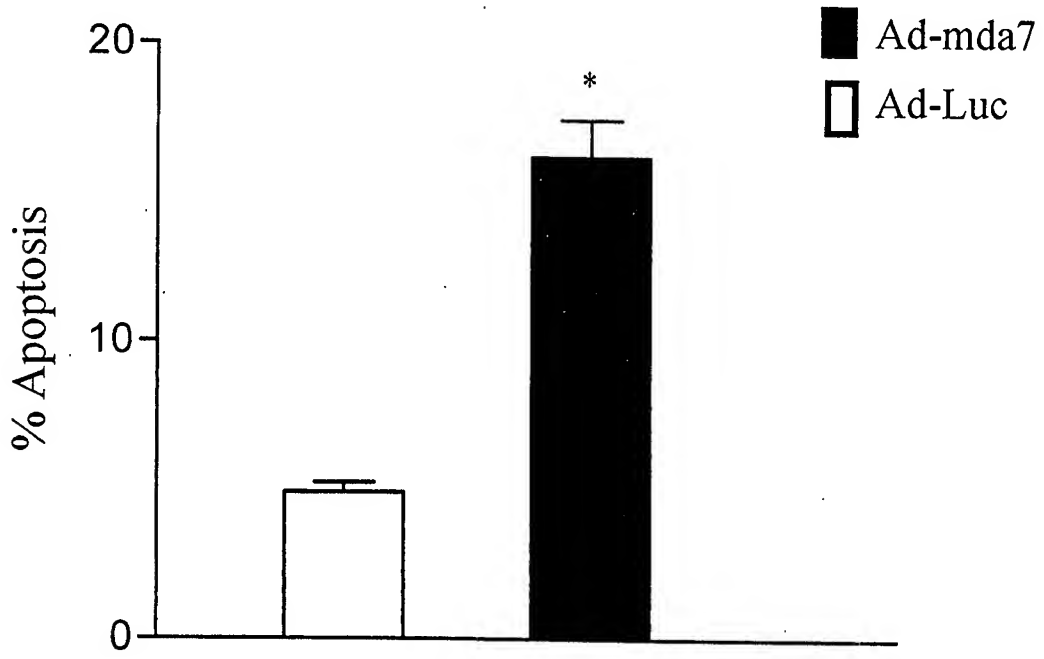


FIG. 32B

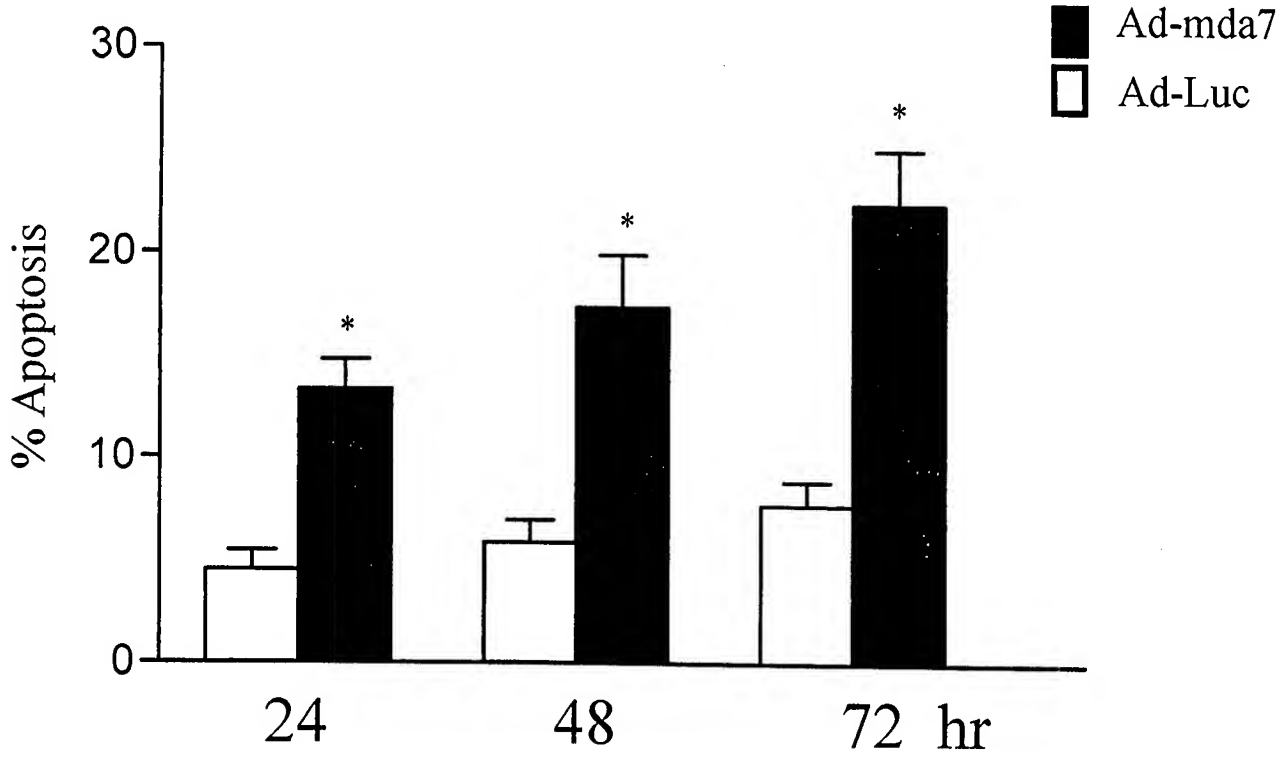


FIG. 32C

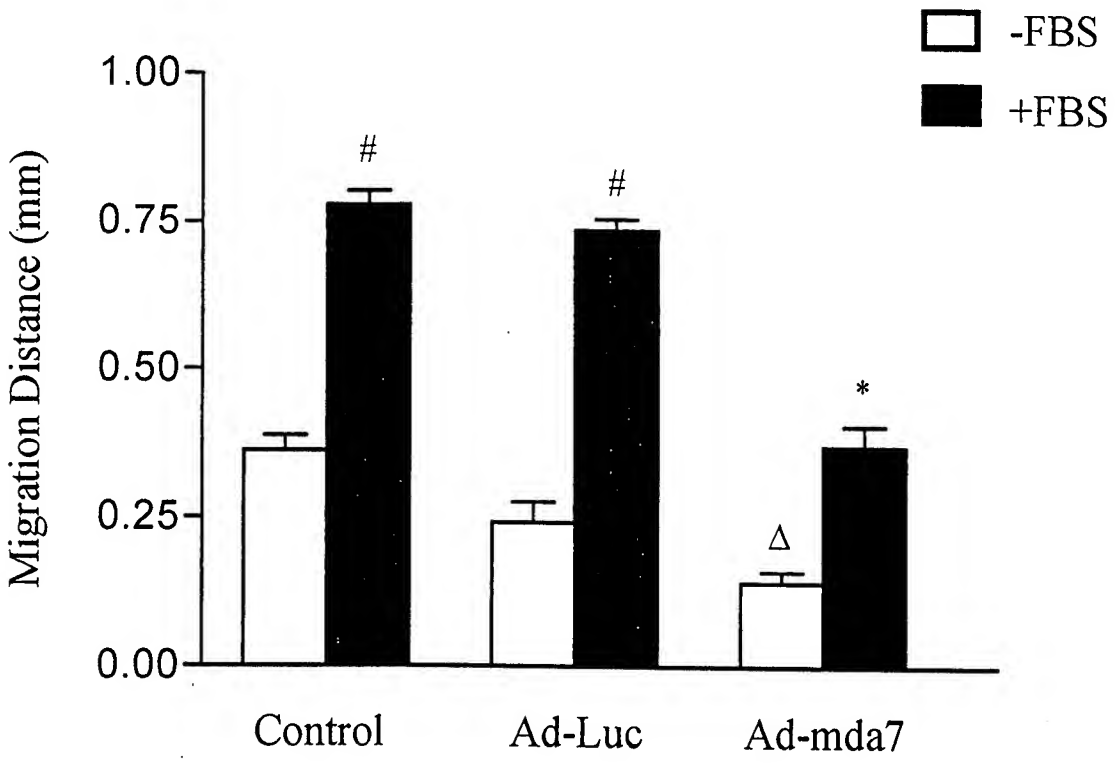

-FBS
+FBS
Migration Distance (mm)
1.00
0.75
0.50
0.25
0.00
#
#
*
Δ
Control
Ad-Luc
Ad-mda7

FIG. 33

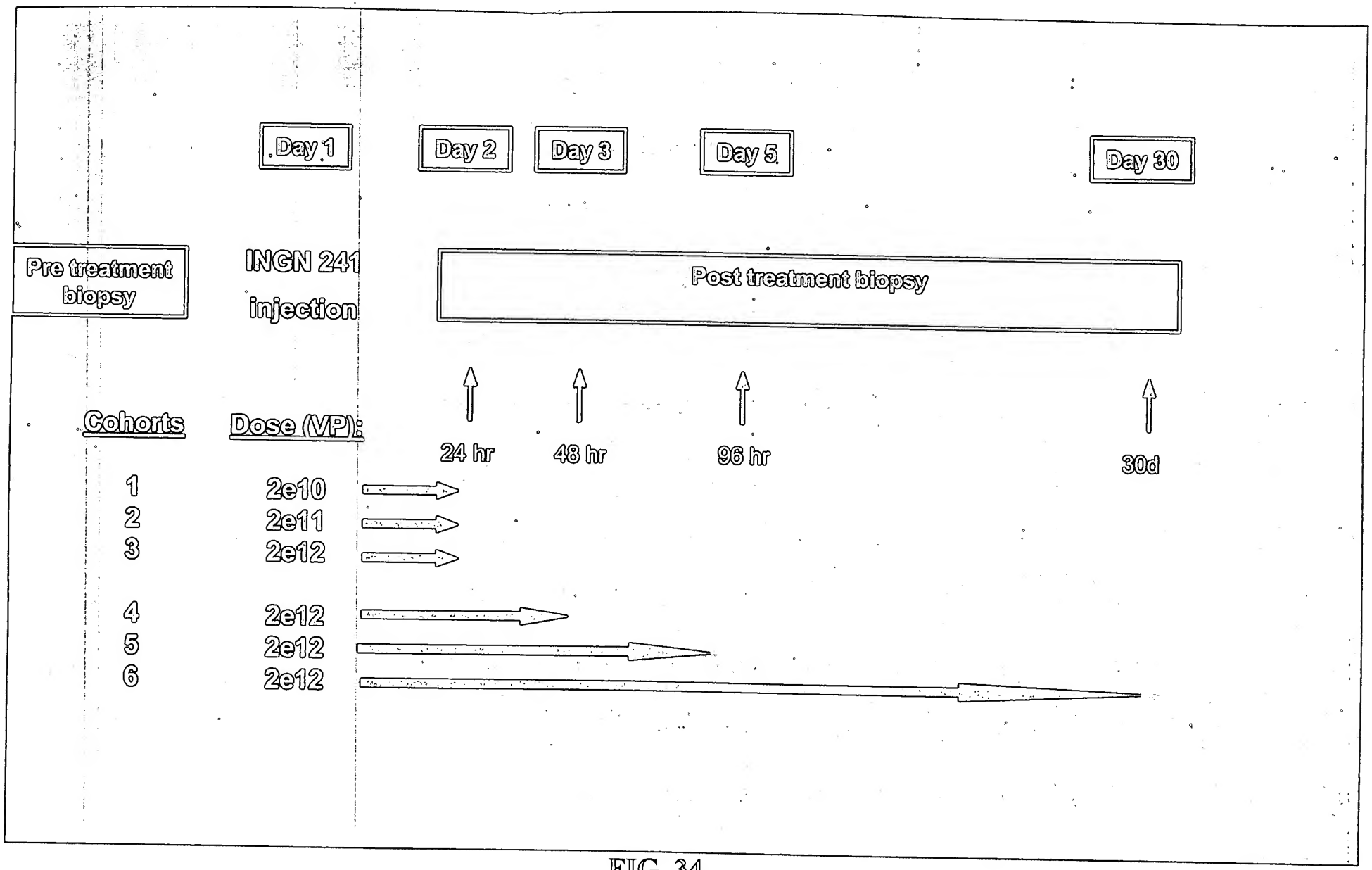

Day 1
Day 2
Day 3
Day 5
Day 30
Pre treatment biopsy
INGN 241 injection
Post treatment biopsy
Cohorts
Dose (VP):
24 hr
48 hr
96 hr
30d
1
2
3
4
5
6
2e10
2e11
2e12
2e12
2e12
2e12

FIG. 34

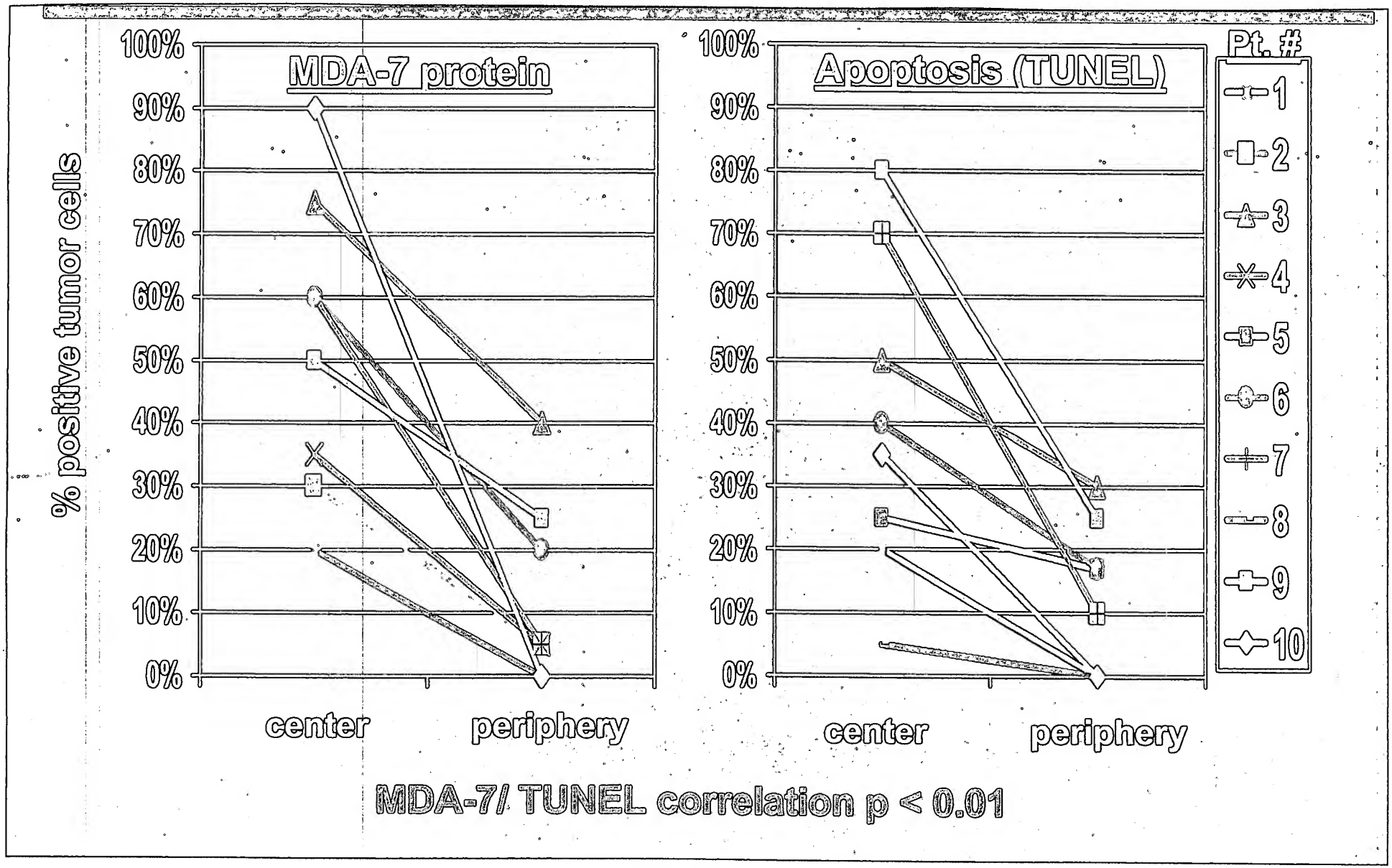

% positive tumor cells
MDA-7 protein
Apoptosis (TUNEL)
Pt. #
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
center
periphery
1
2
3
4
5
6
7
8
9
10
MDA-7/ TUNEL correlation p < 0.01

FIG. 35

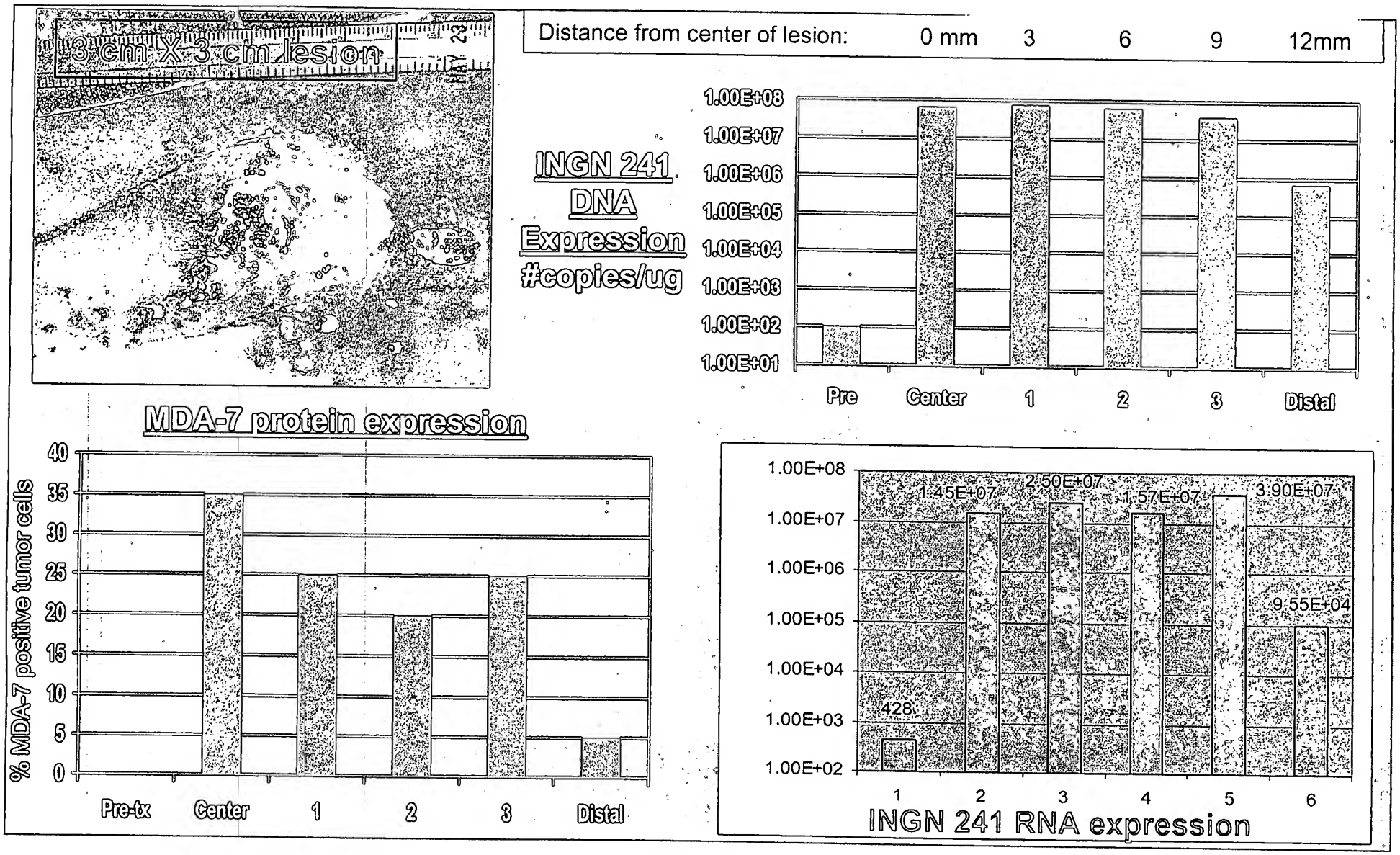

3 cm X 3 cm lesion
Distance from center of lesion: 0 mm 3 6 9 12mm
INGN 241 DNA Expression #copies/ug
1.00E+08
1.00E+07
1.00E+06
1.00E+05
1.00E+04
1.00E+03
1.00E+02
1.00E+01
Pre
Center
1
2
3
Distal
MDA-7 protein expression
% MDA-7 positive tumor cells
40
35
30
25
20
15
10
5
0
Pre-tx
Center
1
2
3
Distal
1.00E+08
1.00E+07
1.00E+06
1.00E+05
1.00E+04
1.00E+03
1.00E+02
1.45E+07
2.50E+07
1.57E+07
3.90E+07
9.55E+04
428
1
2
3
4
5
6
INGN 241 RNA expression

FIG. 36

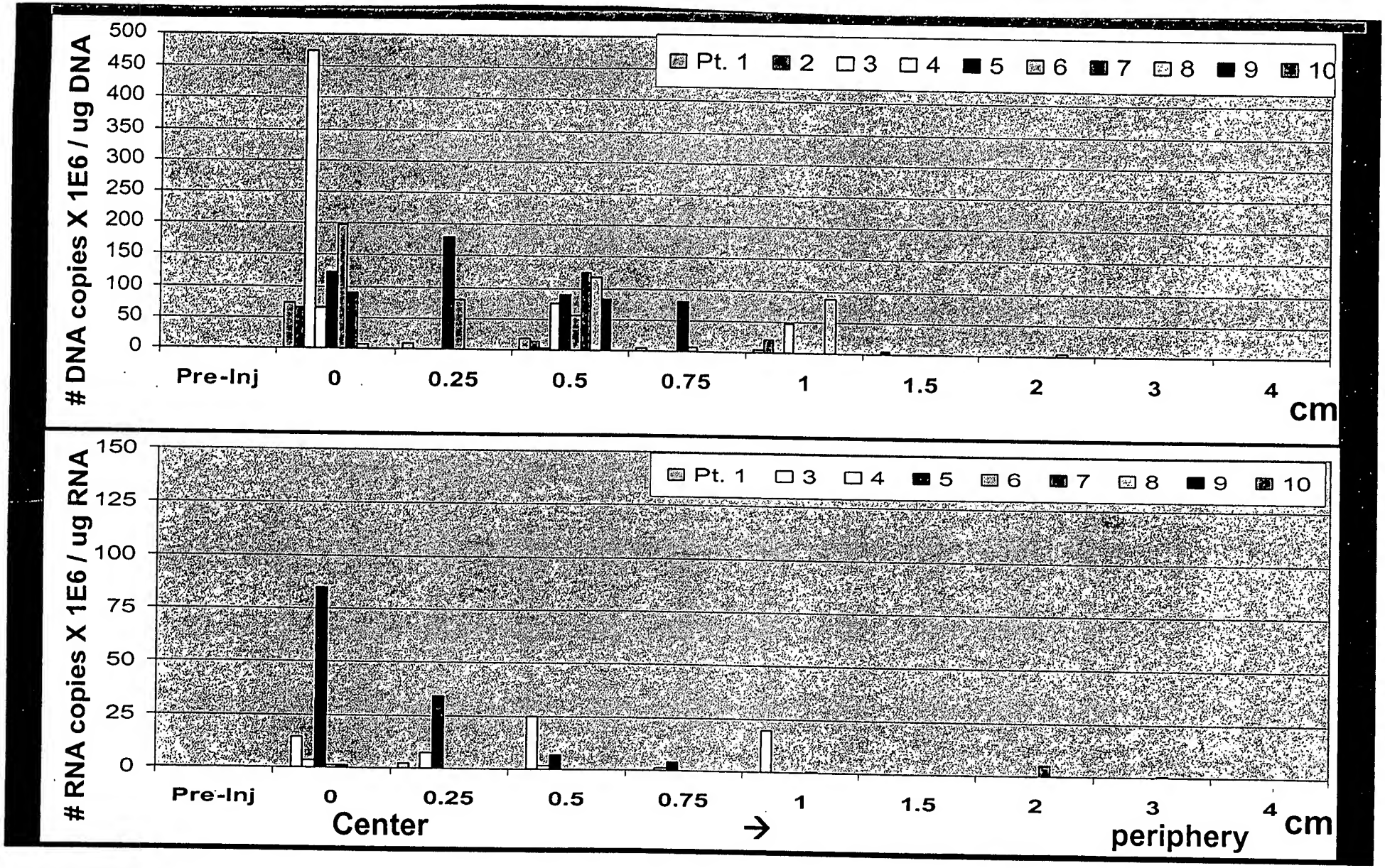

500
450
400
350
300
250
200
150
100
50
0
DNA copies X 1E6 / ug DNA
Pt. 1
2
3
4
5
6
7
8
9
10
Pre-Inj
0
0.25
0.5
0.75
1
1.5
2
3
4
cm
150
125
100
75
50
25
0
RNA copies X 1E6 / ug RNA
Pt. 1
3
4
5
6
7
8
9
10
Pre-Inj
0
0.25
0.5
0.75
1
1.5
2
3
4
cm
Center
periphery

FIG. 37

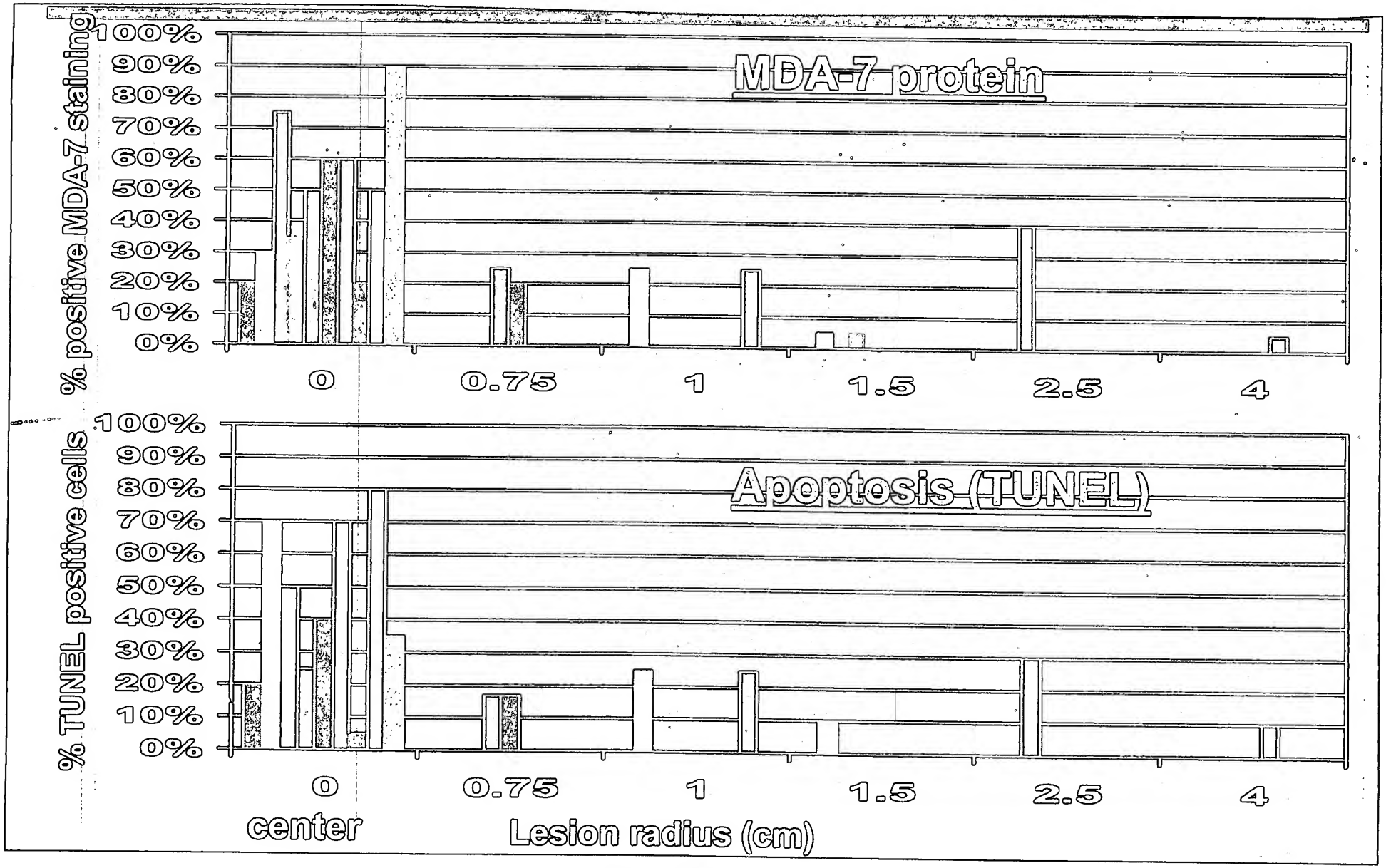

MDA-7 protein
% positive MDA-7 staining
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
0.75
1
1.5
2.5
4
Apoptosis (TUNEL)
% TUNEL positive cells
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
0.75
1
1.5
2.5
4
center
Lesion radius (cm)

FIG. 38

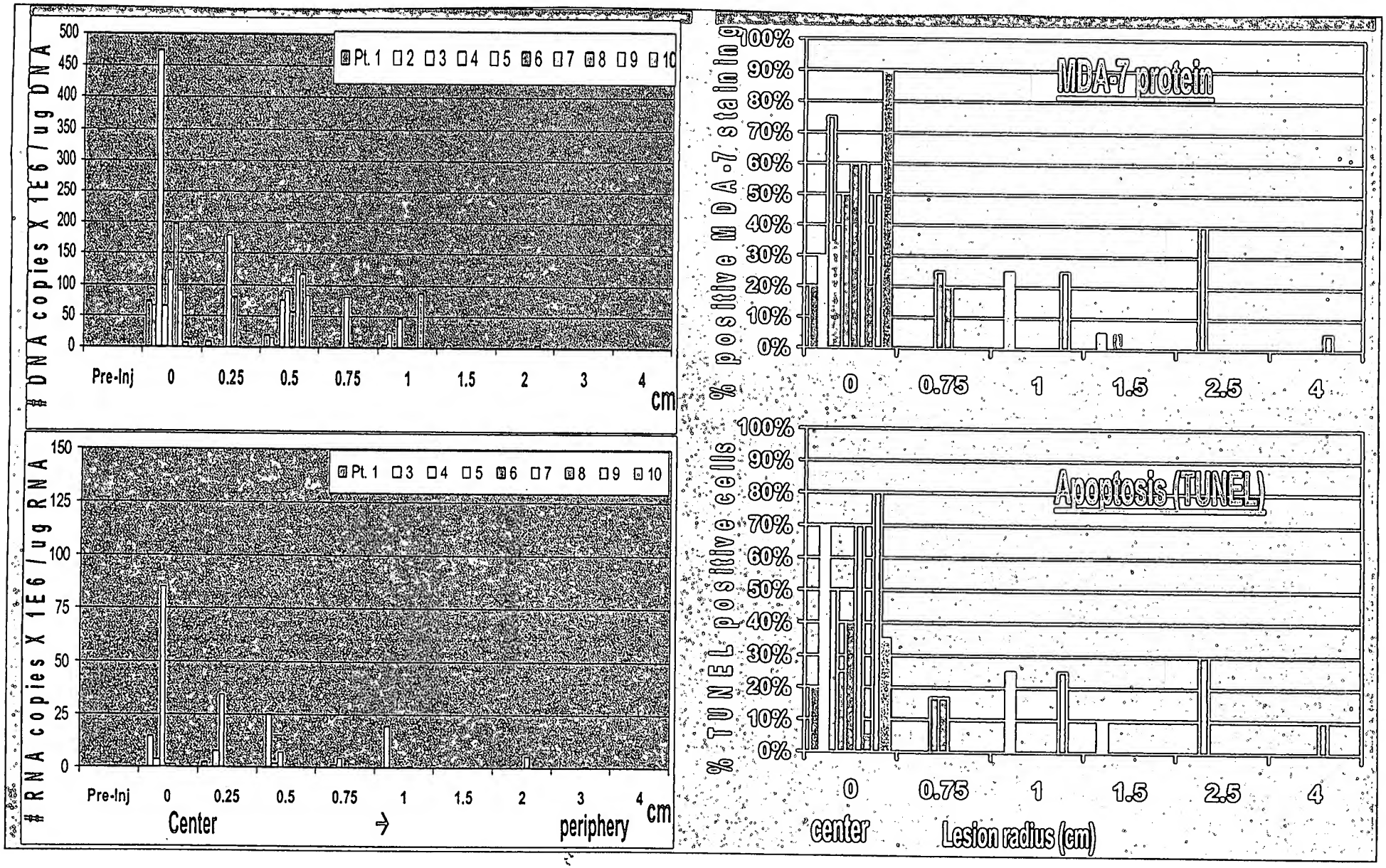

DNA copies X 1E6 / ug DNA
Pt. 1 2 3 4 5 6 7 8 9 10
Pre-Inj 0 0.25 0.5 0.75 1 1.5 2 3 4 cm
RNA copies X 1E6 / ug RNA
Pt. 1 3 4 5 6 7 8 9 10
Pre-Inj 0 0.25 0.5 0.75 1 1.5 2 3 4 cm
Center
periphery
% positive MDA-7 staining
MDA-7 protein
0 0.75 1 1.5 2.5 4
% TUNEL positive cells
Apoptosis (TUNEL)
0 0.75 1 1.5 2.5 4
center
Lesion radius (cm)

FIG. 39

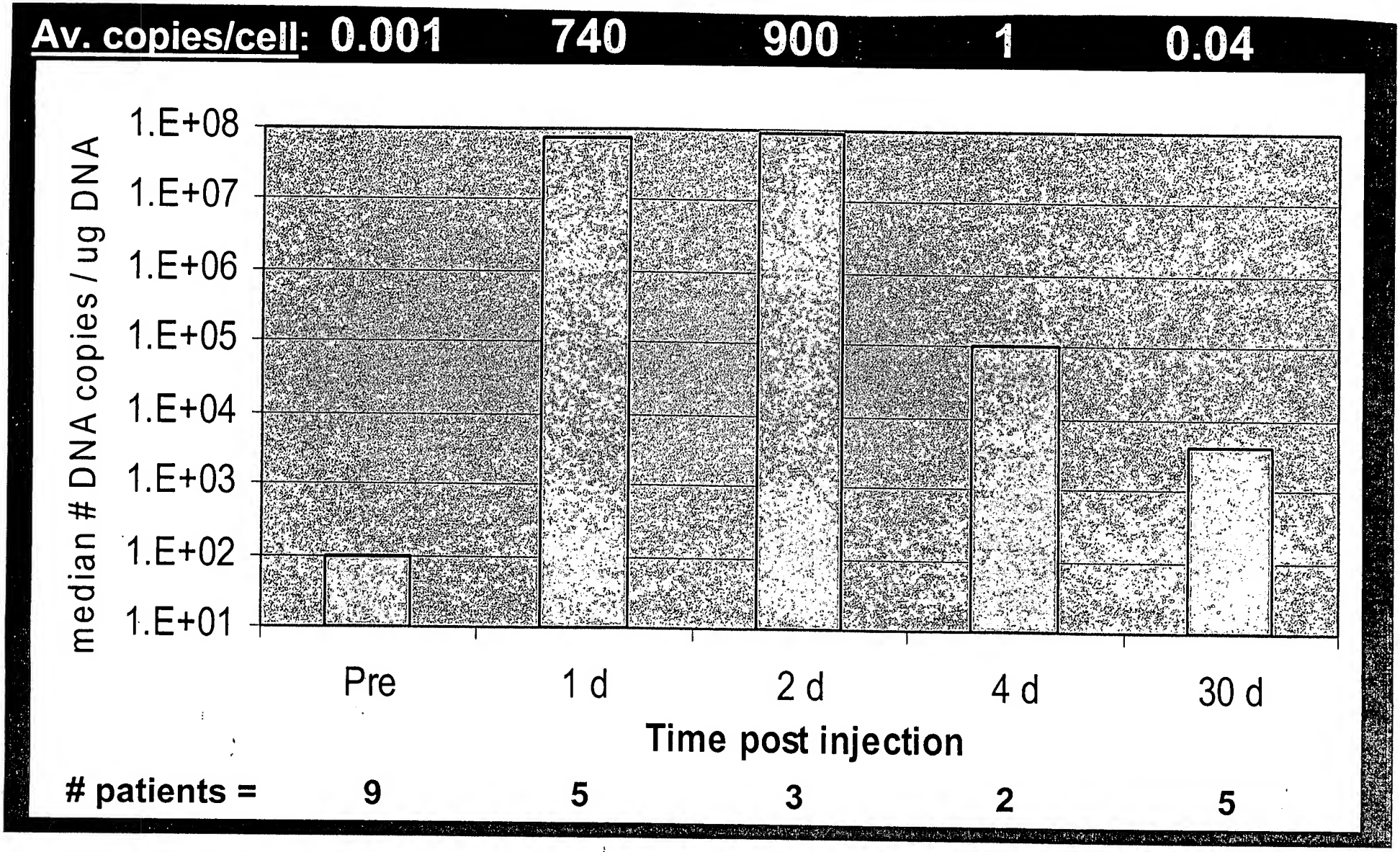

Av. copies/cell: 0.001 740 900 1 0.04
median # DNA copies / ug DNA
1.E+08
1.E+07
1.E+06
1.E+05
1.E+04
1.E+03
1.E+02
1.E+01
Pre
1 d
2 d
4 d
30 d
Time post injection
patients = 9 5 3 2 5

FIG. 40

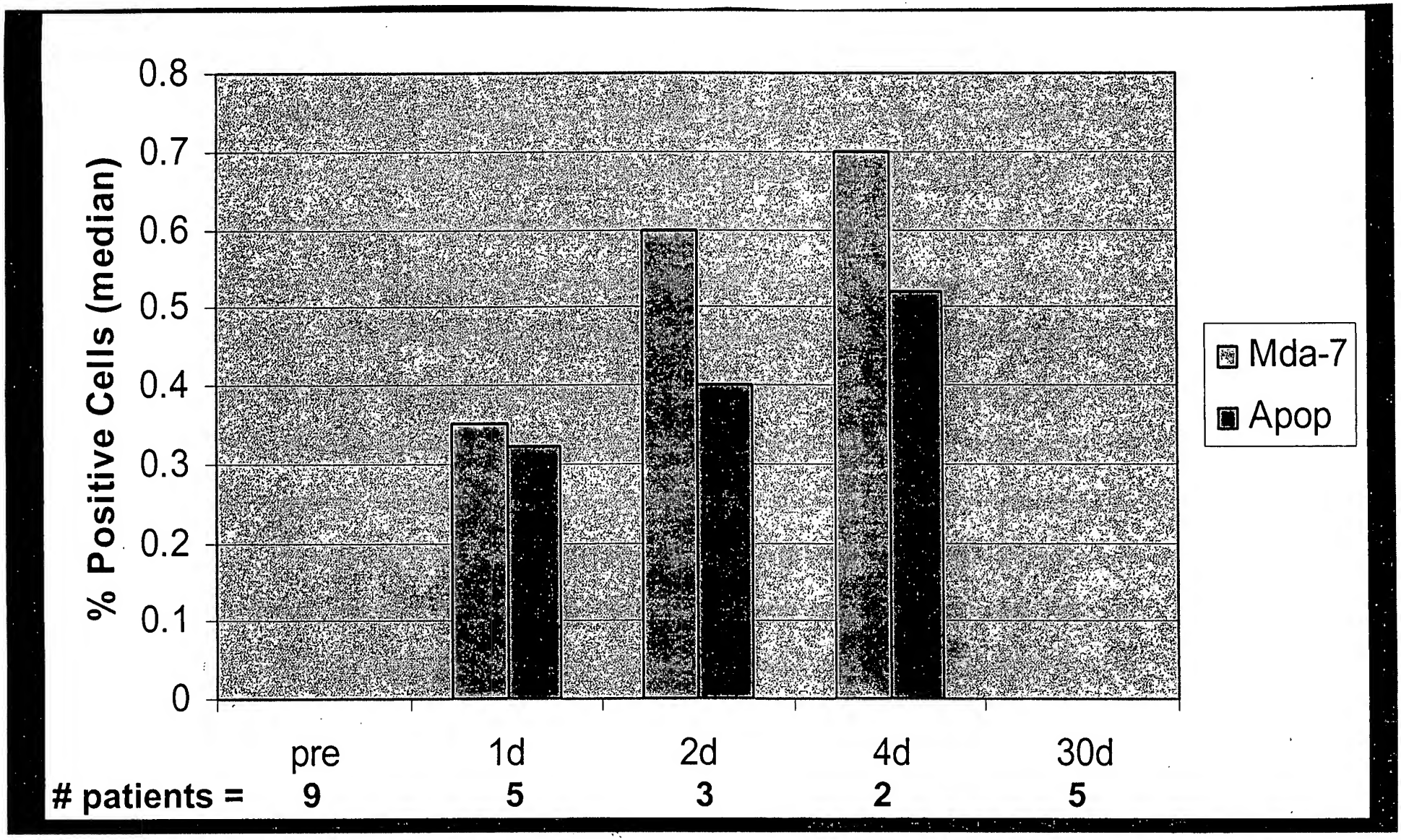

0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
% Positive Cells (median)
Mda-7
Apop
pre
1d
2d
4d
30d
patients =
9
5
3
2
5

FIG. 41

Single Dose (2E12 vp)

Patient	Primary Histology	# injections	Clinical Activity (Y/N) Local	Remote	Comment
71	Renal Cell Ca	1	N	N	Withdrew prior to day 30
72	TCC Bladder	1	N	N	
73	Melanoma	1	N	N	
74	Colo-Rectal	1	N	N	
75	SCCHN	1	N	N	Withdrew prior to day 30
76	SCCHN	1	N	N	
77	SCCHN	1	N	N	

Repeat Dose (2E12 vp biweekly x3)

81	AdenoCa	3	-	-	Withdrew
83	Melanoma	12	Y*	Y**	CR
84	Melanoma	12	N	N	Stable Disease
85	SCCHN	6	Y	N	Central necrosis
86	NSCLC	3	-	-	Not eval
87	SCCHN	6	Y	pending	On study
88	Melanoma	6	Y	pending	On study

*Three lesions treated consecutively: pCR in 1st, clinCR in 2nd, regression in 3rd

**marked erythema around remote cutaneous lesion

FIG. 42

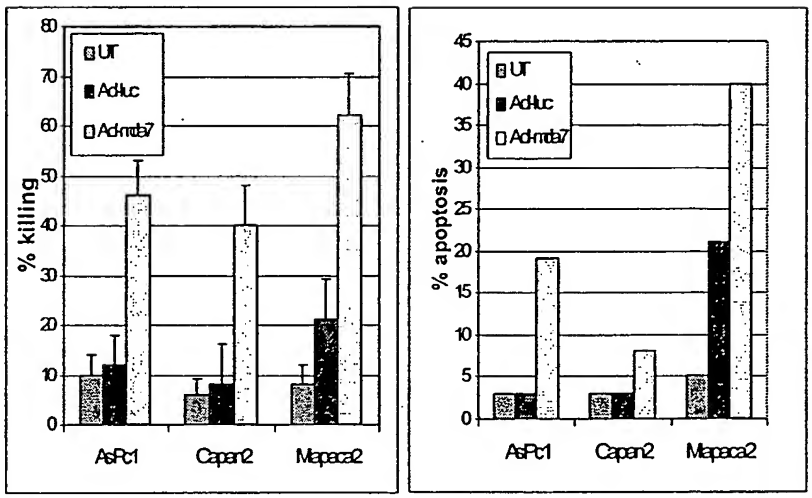

% killing
UT
Adluc
Admda7
AsPc1
Capan2
Mapaca2
% apoptosis
UT
Adluc
Admda7
AsPc1
Capan2
Mapaca2

FIG. 43

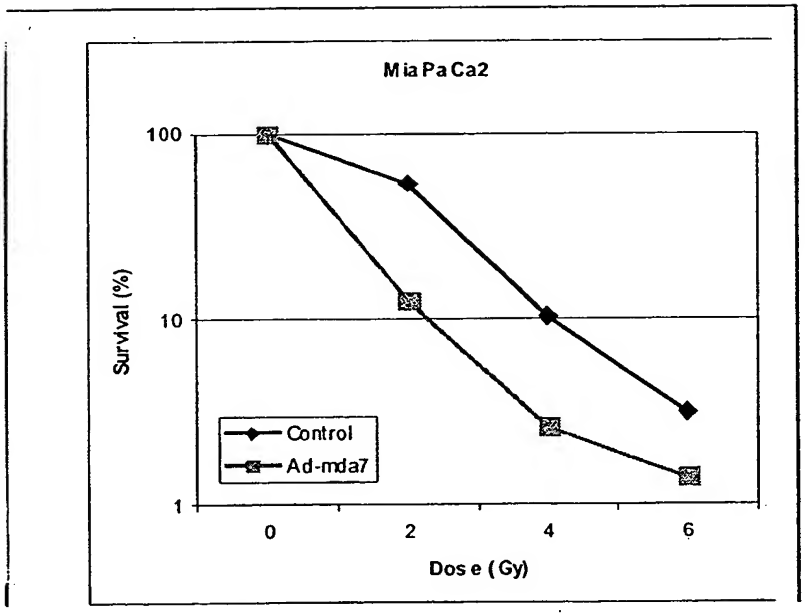


FIG. 44

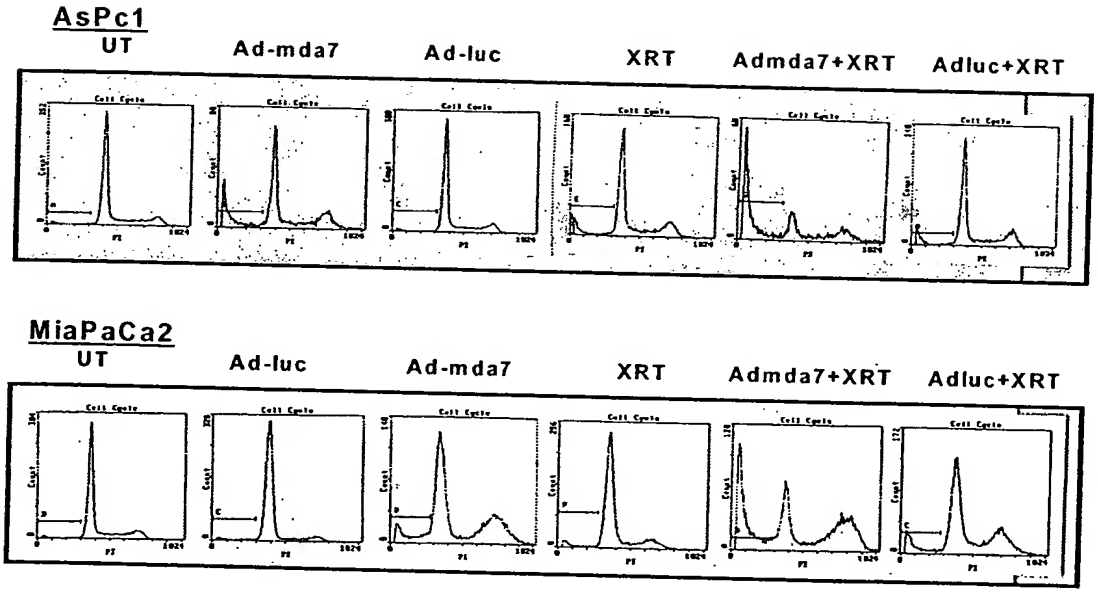

AsPc1
UT
Ad-mda7
Ad-luc
XRT
Admda7+XRT
Adluc+XRT
MiaPaCa2
UT
Ad-luc
Ad-mda7
XRT
Admda7+XRT
Adluc+XRT

FIG. 45

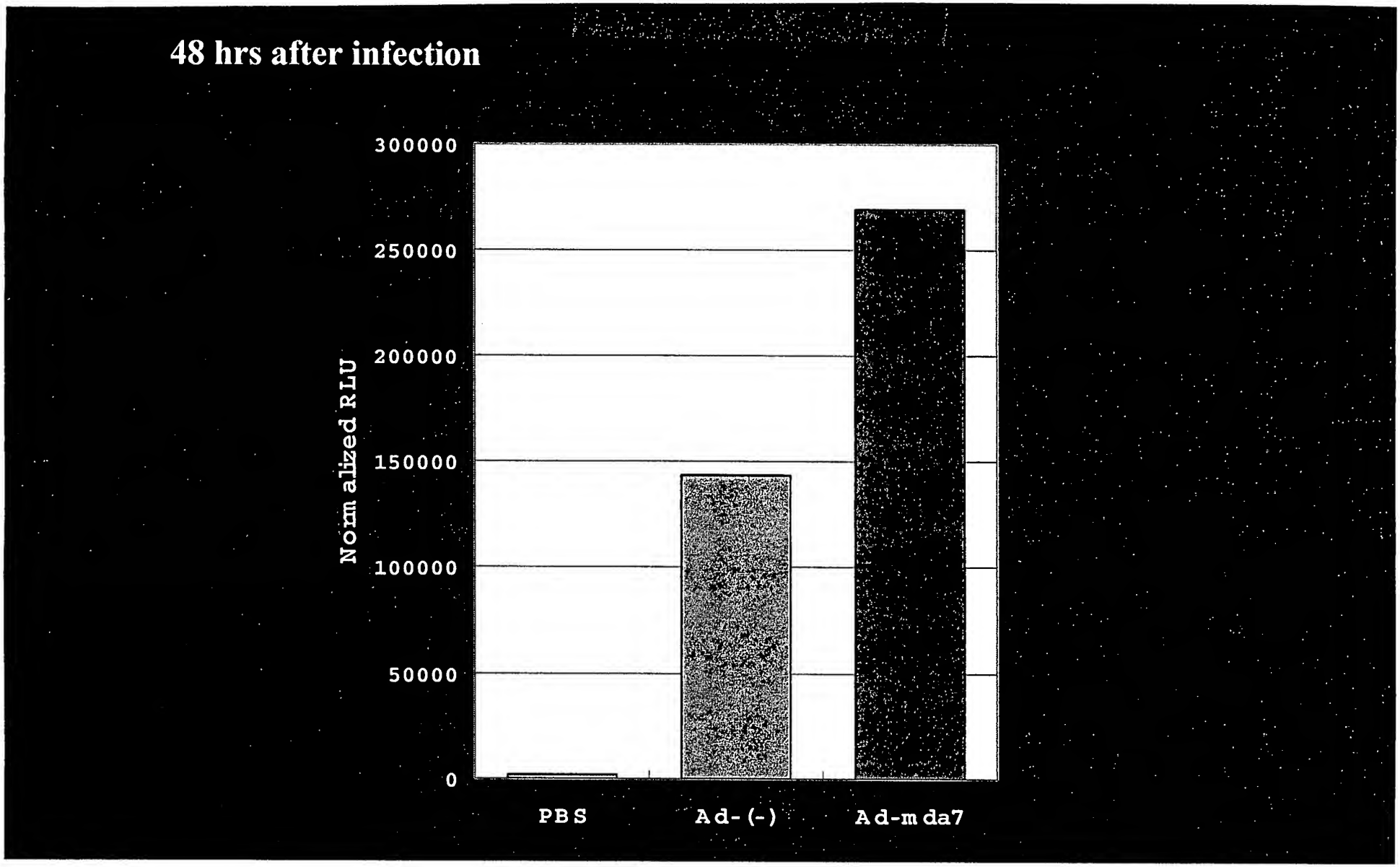

48 hrs after infection
300000
250000
200000
150000
100000
50000
0
Normalized RLU
PBS
Ad-(-)
Ad-mda7

FIG. 46

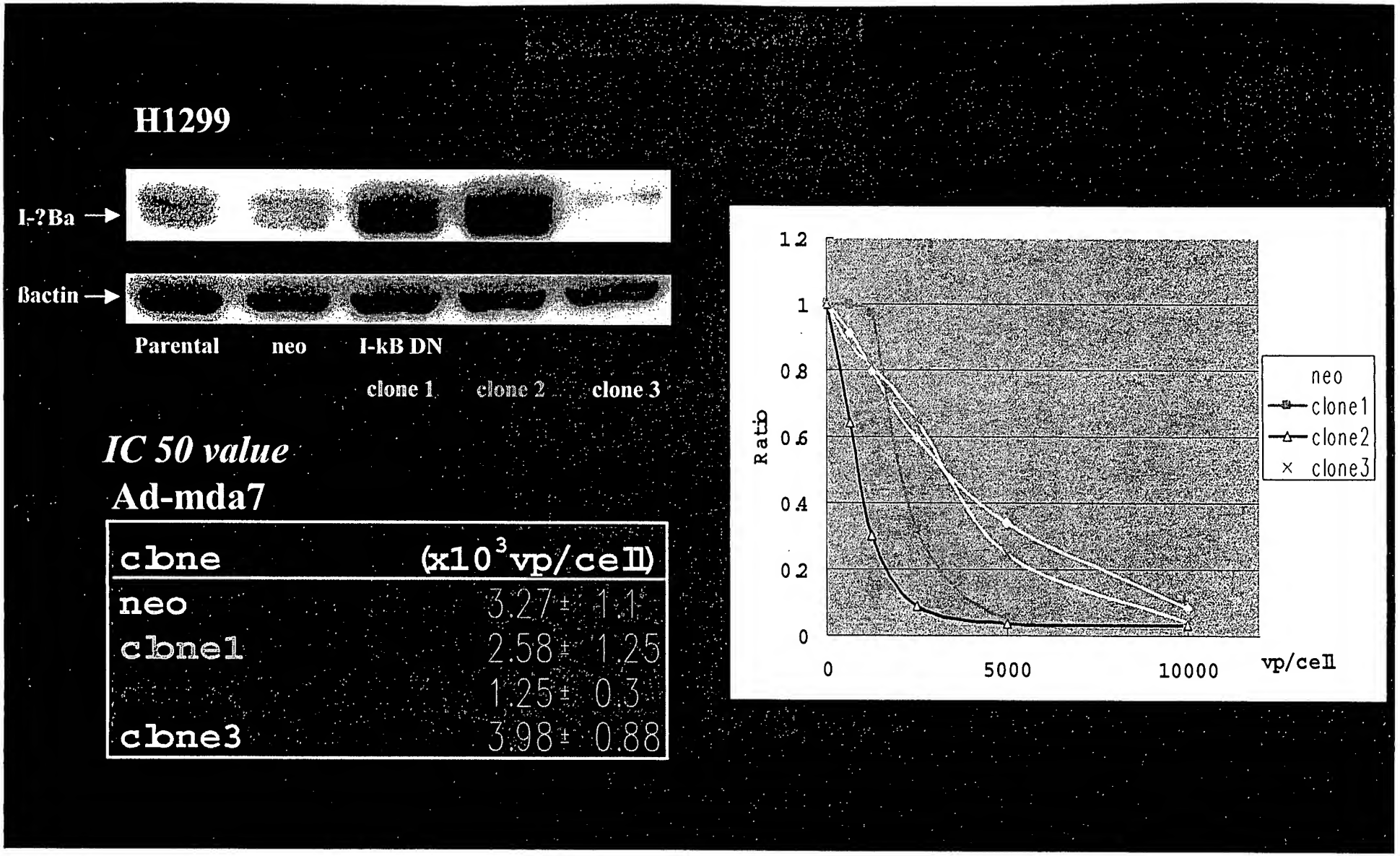

H1299
I-?Ba
ßactin
Parental
neo
I-kB DN
clone 1
clone 2
clone 3
IC 50 value
Ad-mda7
cbne (x10³vp/cell)
neo 3.27± 1.1
cbne1 2.58± 1.25
1.25± 0.3
cbne3 3.98± 0.88
Ratio
1.2
1
0.8
0.6
0.4
0.2
0
0
5000
10000
vp/cell
neo
clone1
clone2
clone3

FIG. 47

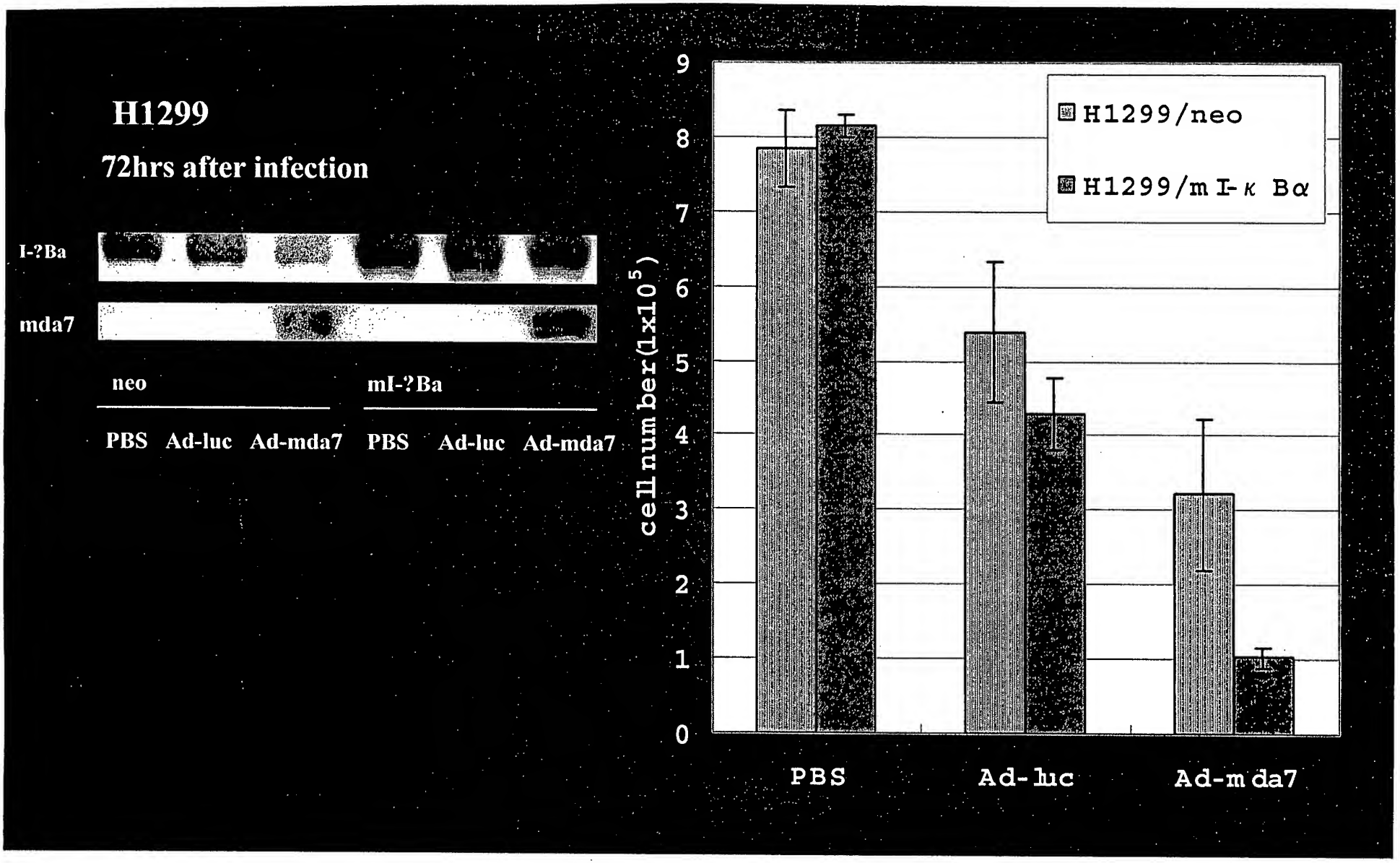

H1299
72hrs after infection
I-?Ba
mda7
neo
mI-?Ba
PBS
Ad-luc
Ad-mda7
PBS
Ad-luc
Ad-mda7
cell number(1x10^5)
0
1
2
3
4
5
6
7
8
9
H1299/neo
H1299/mI-κ Bα
PBS
Ad-luc
Ad-mda7

FIG. 48

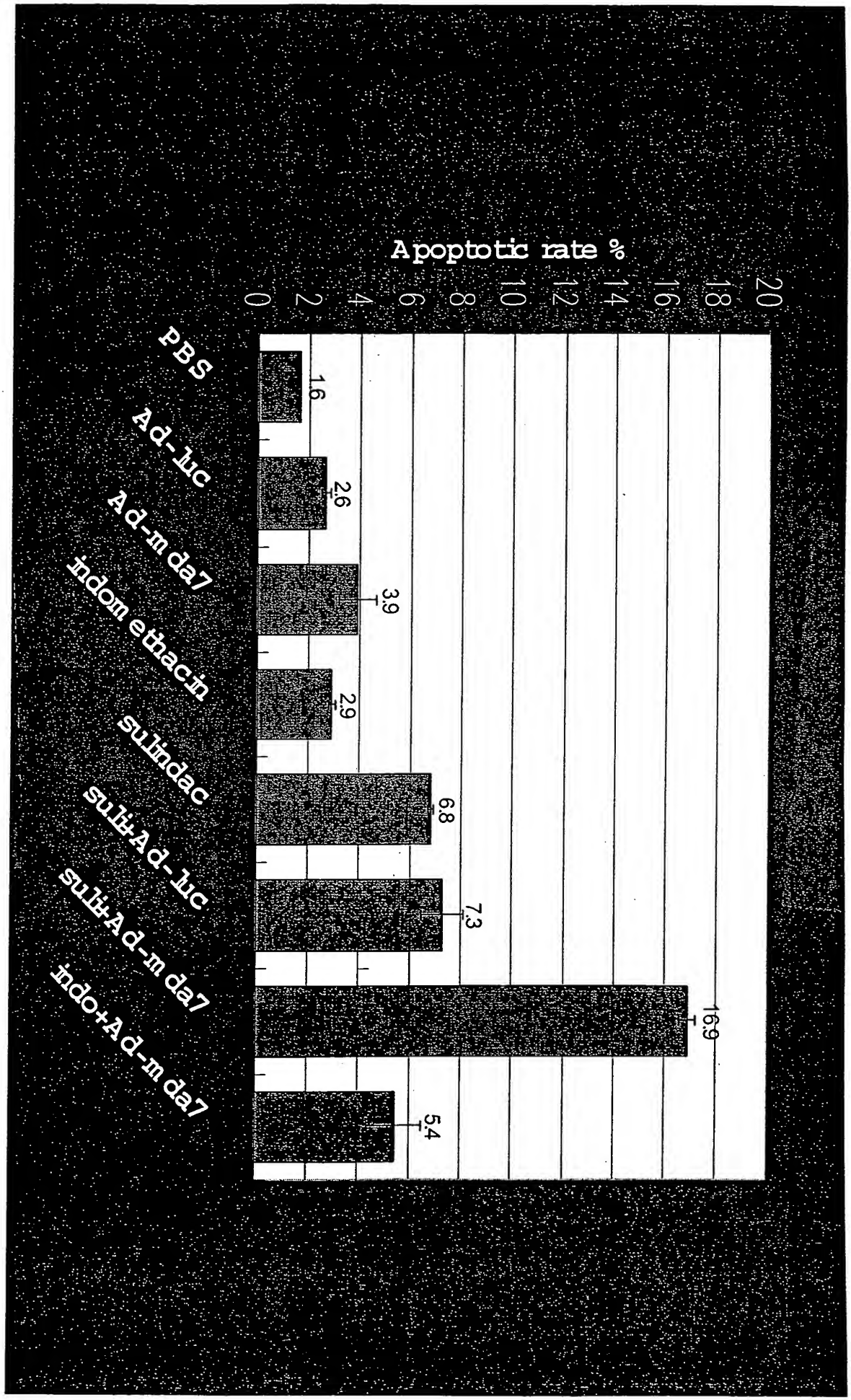

Apoptotic rate %
0
2
4
6
8
10
12
14
16
18
20
1.6
2.6
3.9
2.9
6.8
7.3
16.9
5.4
PBS
Ad-luc
Ad-mda7
indomethacin
sulindac
sulAd-luc
sulAd-mda7
indoAd-mda7

FIG. 49A

A

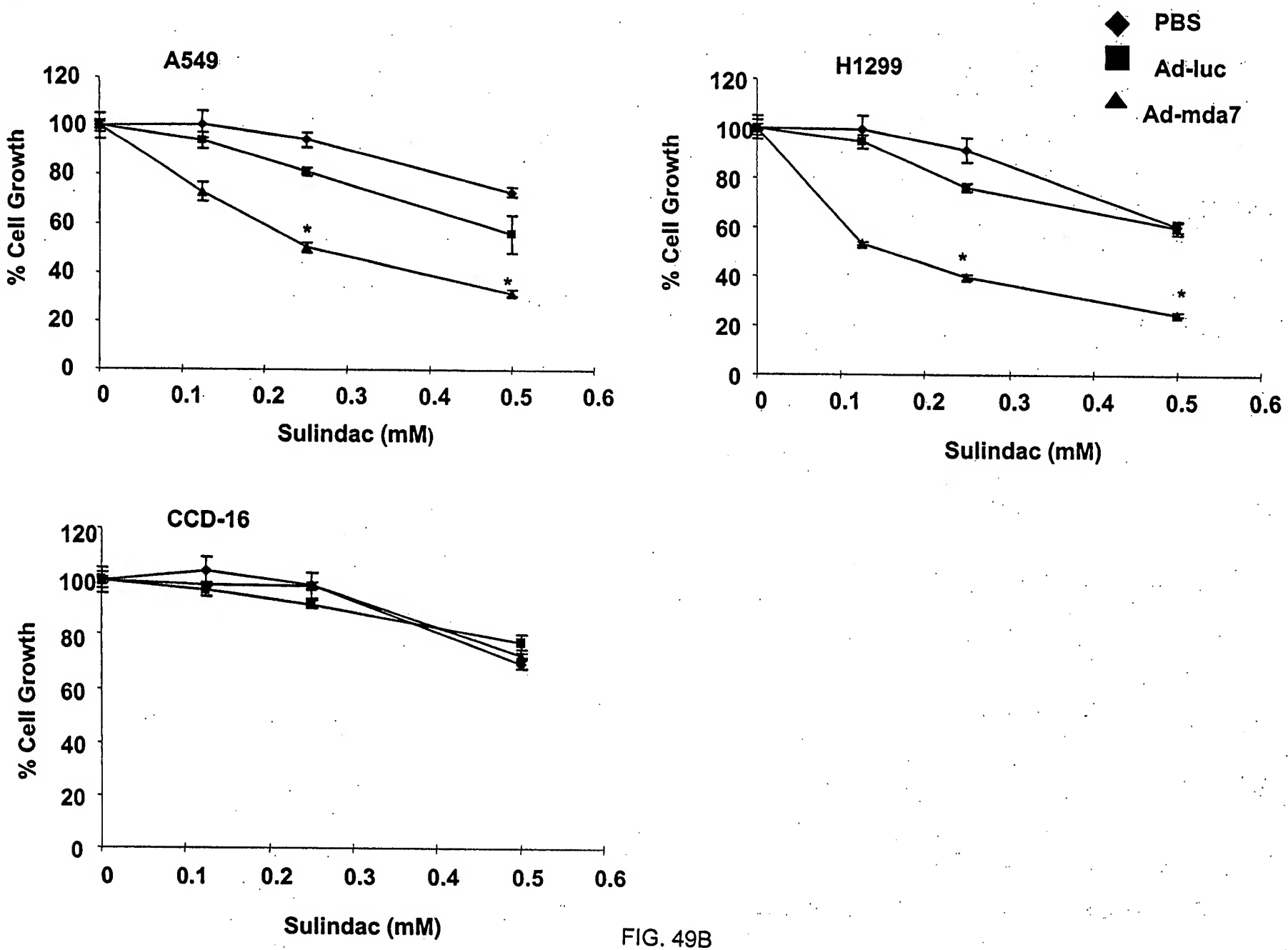

A549
H1299
CCD-16
PBS
Ad-luc
Ad-mda7
% Cell Growth
Sulindac (mM)
0
20
40
60
80
100
120
0.1
0.2
0.3
0.4
0.5
0.6
*

FIG. 49B

B

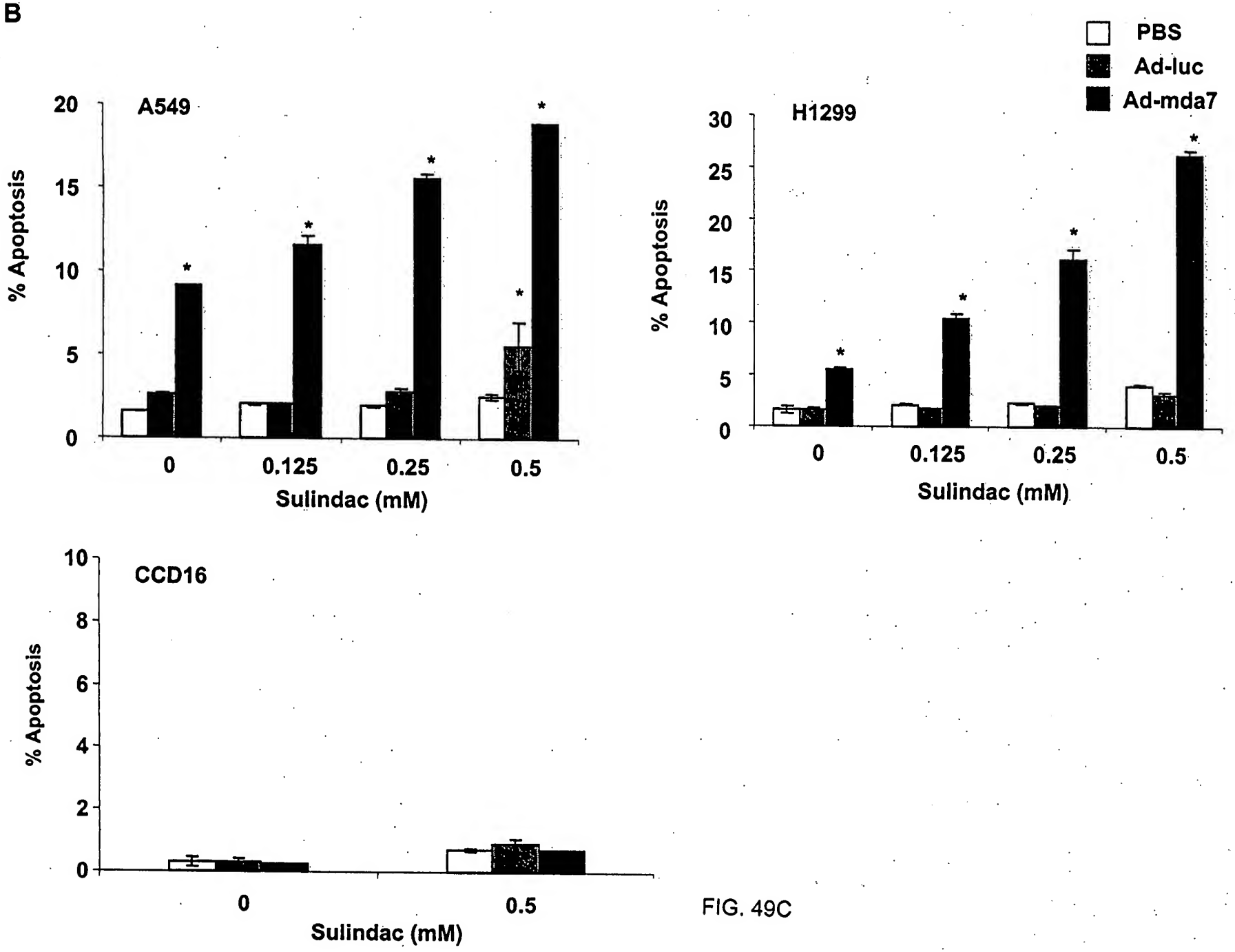

PBS
Ad-luc
Ad-mda7
A549
% Apoptosis
20
15
10
5
0
0
0.125
0.25
0.5
Sulindac (mM)
H1299
% Apoptosis
30
25
20
15
10
5
0
0
0.125
0.25
0.5
Sulindac (mM)
CCD16
% Apoptosis
10
8
6
4
2
0
0
0.5
Sulindac (mM)

FIG. 49C

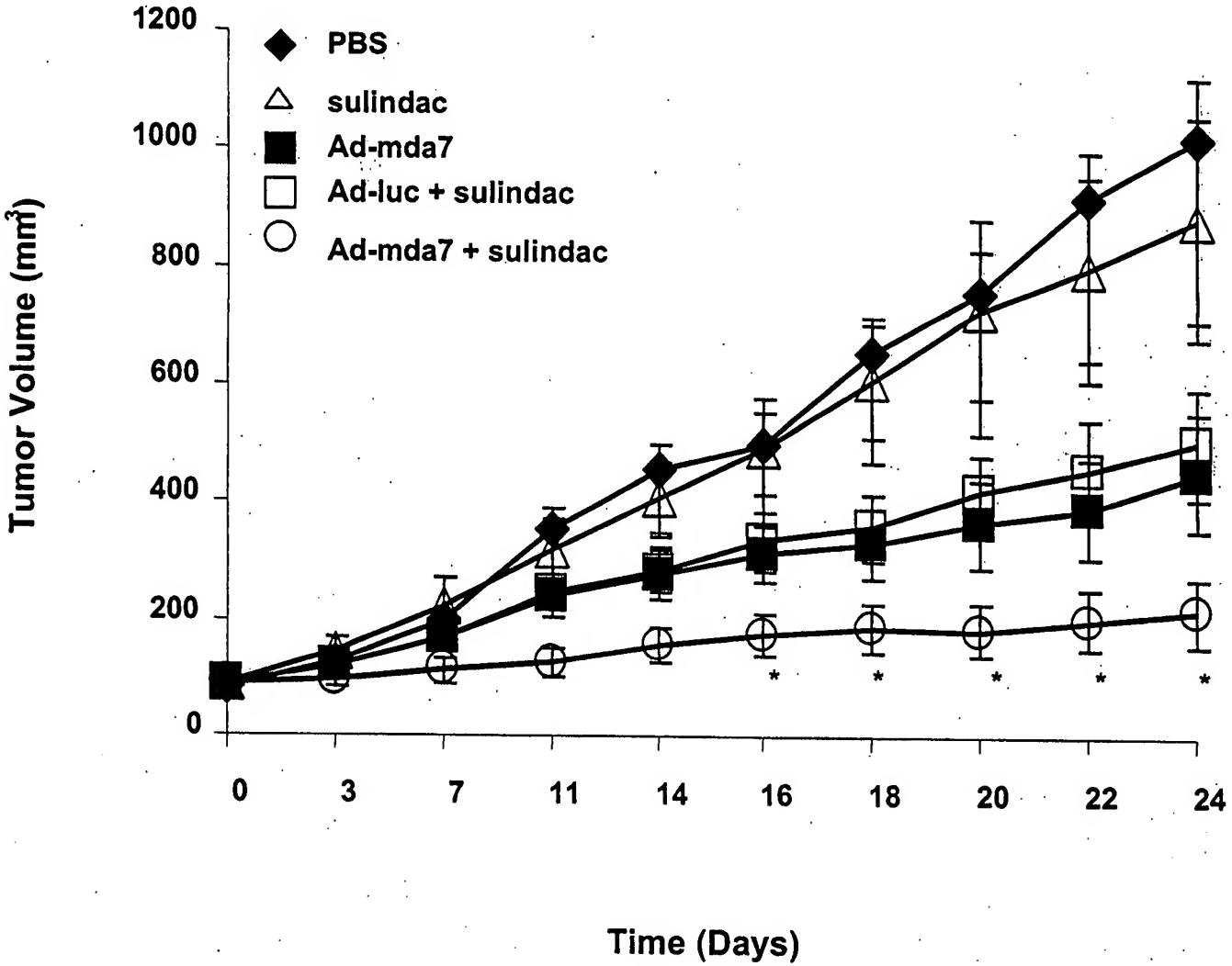

1200
1000
800
600
400
200
0
Tumor Volume (mm3)
PBS
sulindac
Ad-mda7
Ad-luc + sulindac
Ad-mda7 + sulindac
0
3
7
11
14
16
18
20
22
24
Time (Days)

FIG. 49D

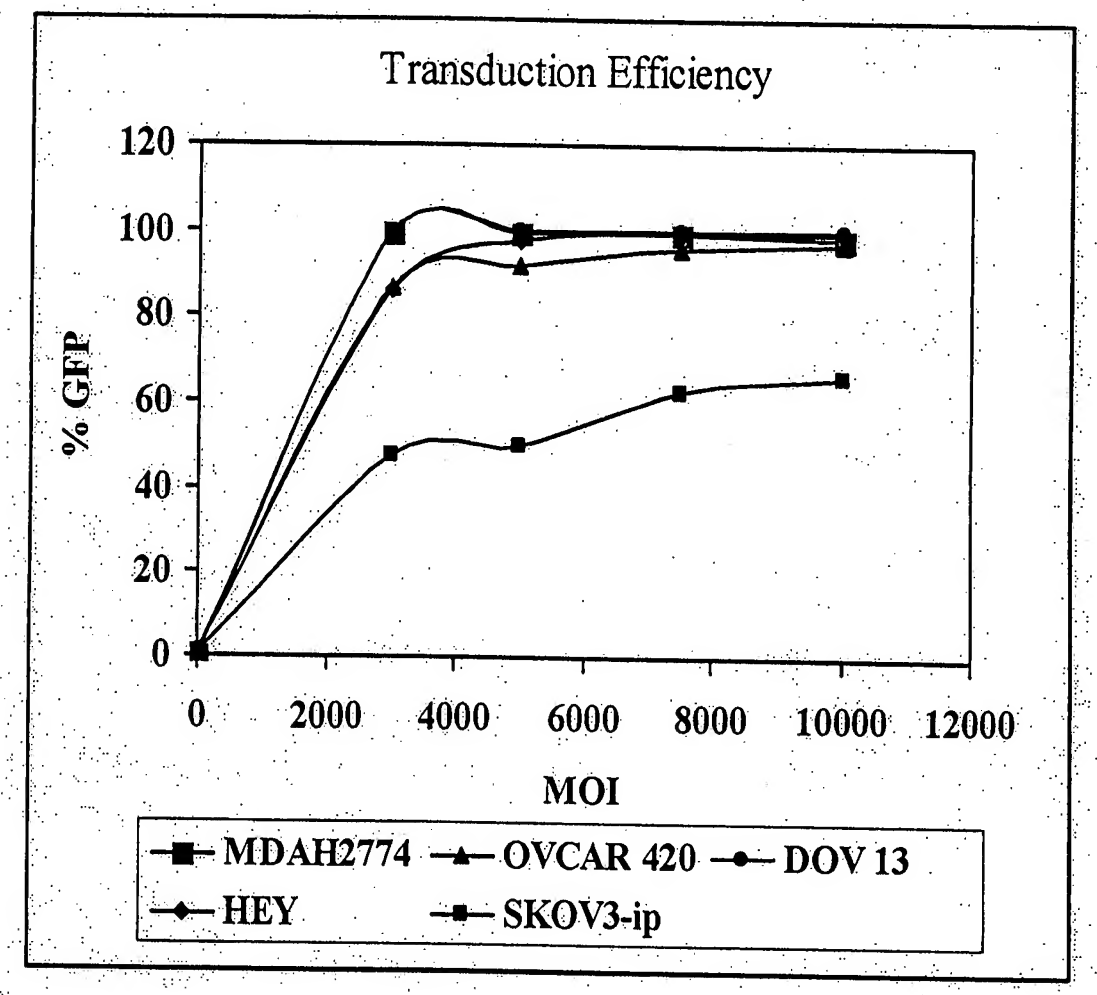
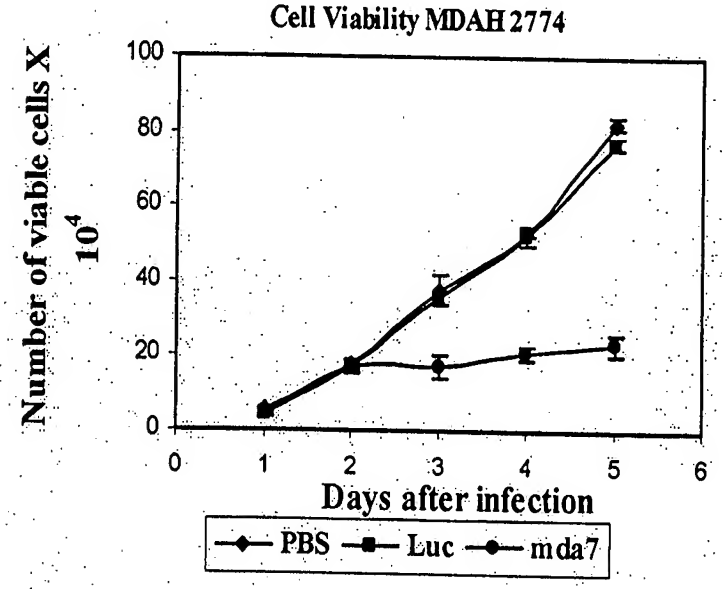

Transduction Efficiency
120
100
80
60
40
20
0
% GFP
0
2000
4000
6000
8000
10000
12000
MOI
MDAH2774
OVCAR 420
DOV 13
HEY
SKOV3-ip

FIG. 50


Cell Viability MDAH 2774
Number of viable cells X 10^4
100
80
60
40
20
0
0
1
2
3
4
5
6
Days after infection
PBS
Luc
mda7

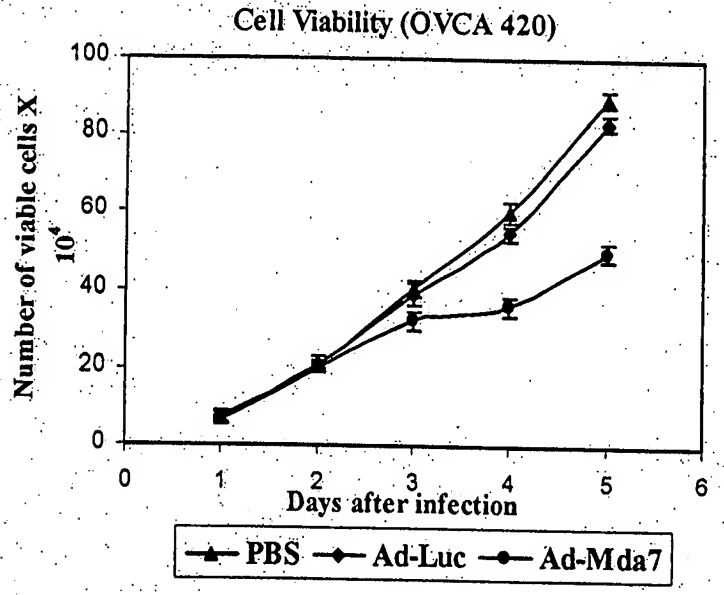
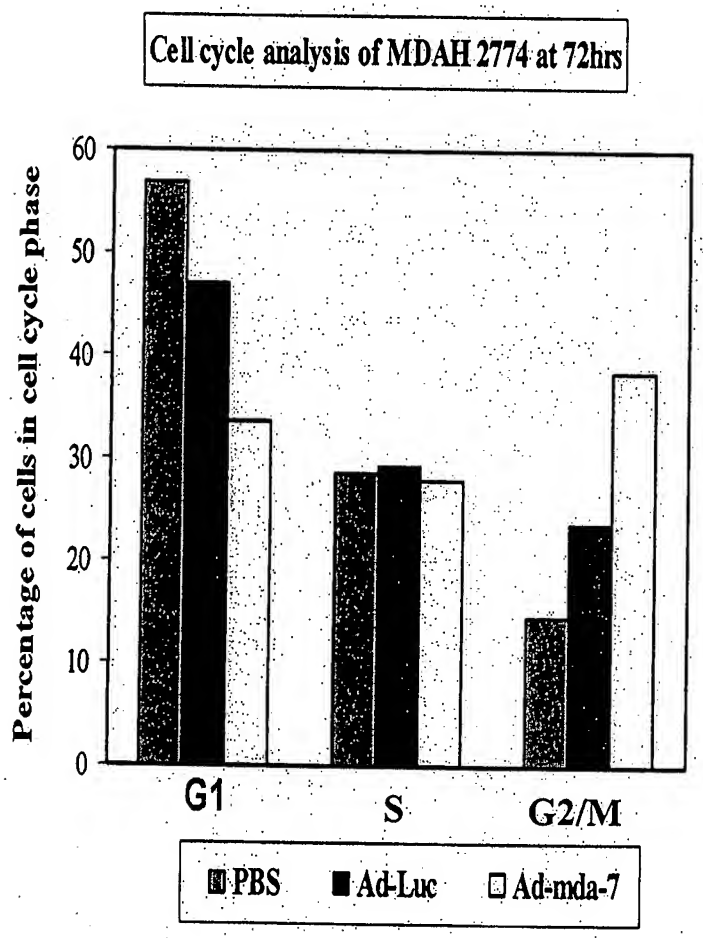

Cell Viability (OVCA 420)
Number of viable cells X 10^4
100
80
60
40
20
0
0
1
2
3
4
5
6
Days after infection
PBS
Ad-Luc
Ad-Mda7

FIG. 51


Cell cycle analysis of MDAH 2774 at 72hrs
Percentage of cells in cell cycle phase
60
50
40
30
20
10
0
G1
S
G2/M
PBS
Ad-Luc
Ad-mda-7

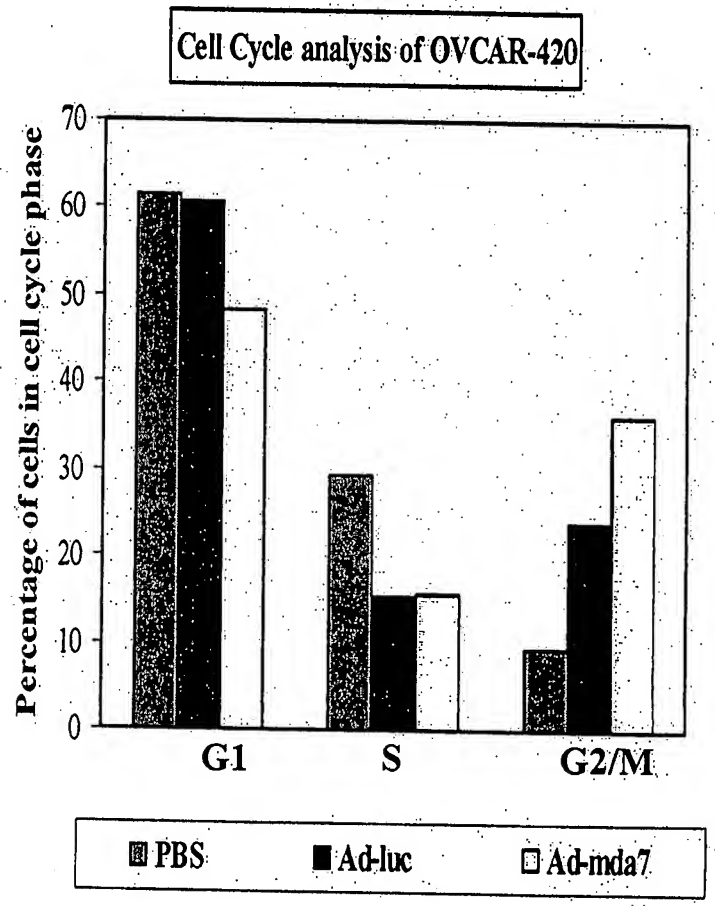

Cell Cycle analysis of OVCAR-420
Percentage of cells in cell cycle phase
70
60
50
40
30
20
10
0
G1
S
G2/M
PBS
Ad-luc
Ad-mda7

FIG. 52

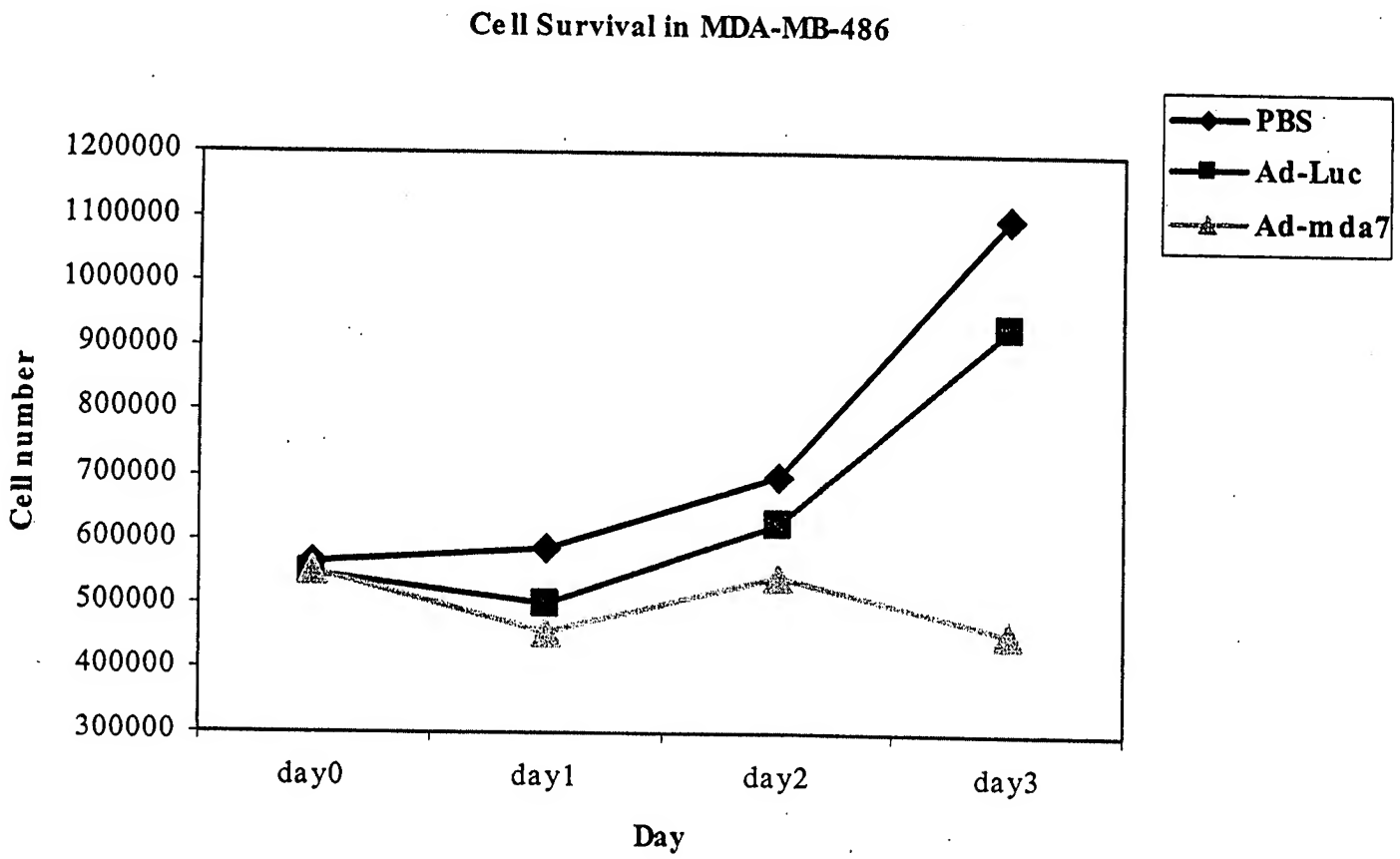

Cell Survival in MDA-MB-486
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
Cell number
day0
day1
day2
day3
Day
PBS
Ad-Luc
Ad-mda7

FIG. 53

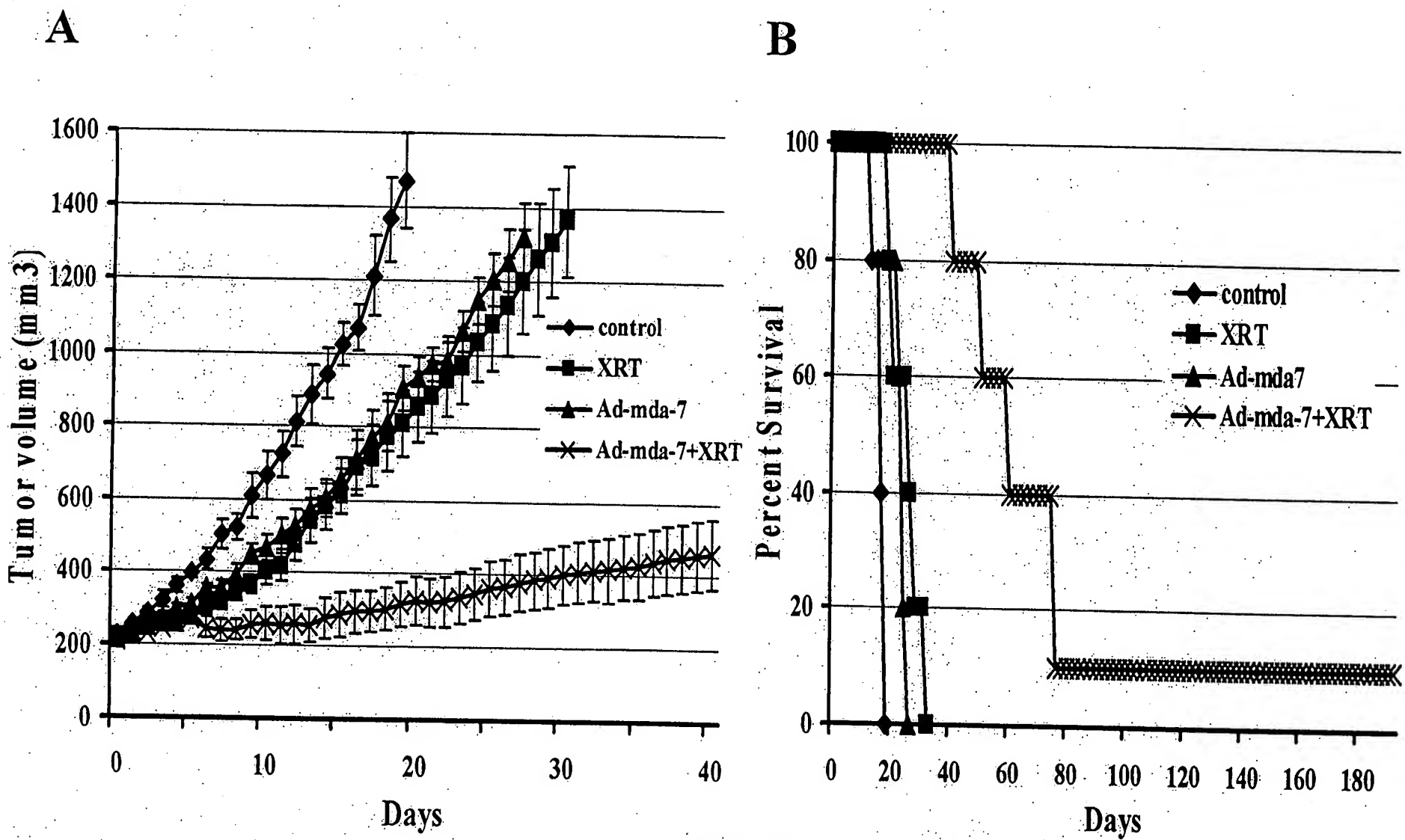

A
B
Tumor volume (mm3)
1600
1400
1200
1000
800
600
400
200
0
0
10
20
30
40
Days
control
XRT
Ad-mda-7
Ad-mda-7+XRT
Percent Survival
100
80
60
40
20
0
0
20
40
60
80
100
120
140
160
180
Days
control
XRT
Ad-mda7
Ad-mda-7+XRT

FIG. 54

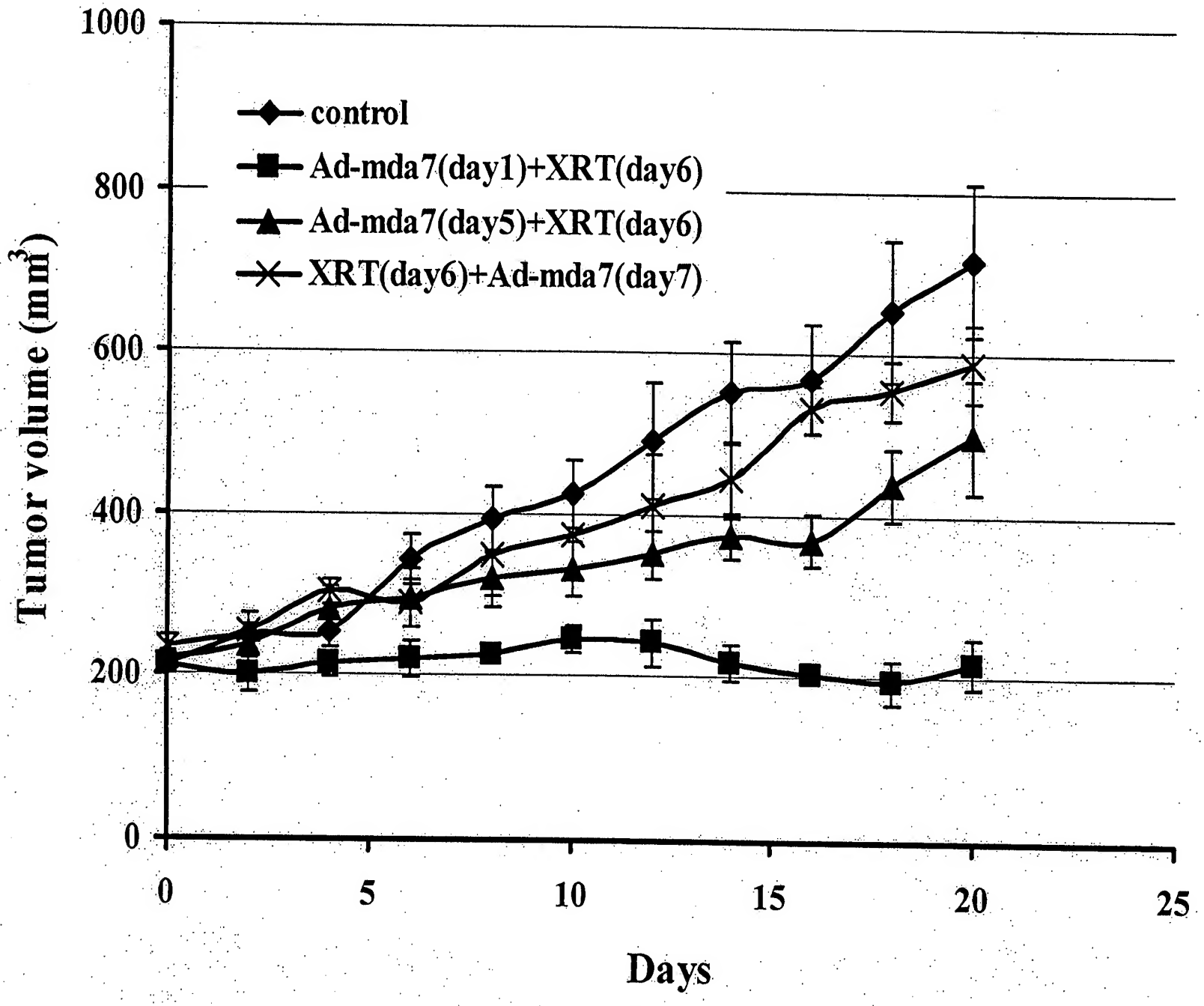

1000
800
600
400
200
0
Tumor volume (mm3)
control
Ad-mda7(day1)+XRT(day6)
Ad-mda7(day5)+XRT(day6)
XRT(day6)+Ad-mda7(day7)
0
5
10
15
20
25
Days

FIG. 55

B

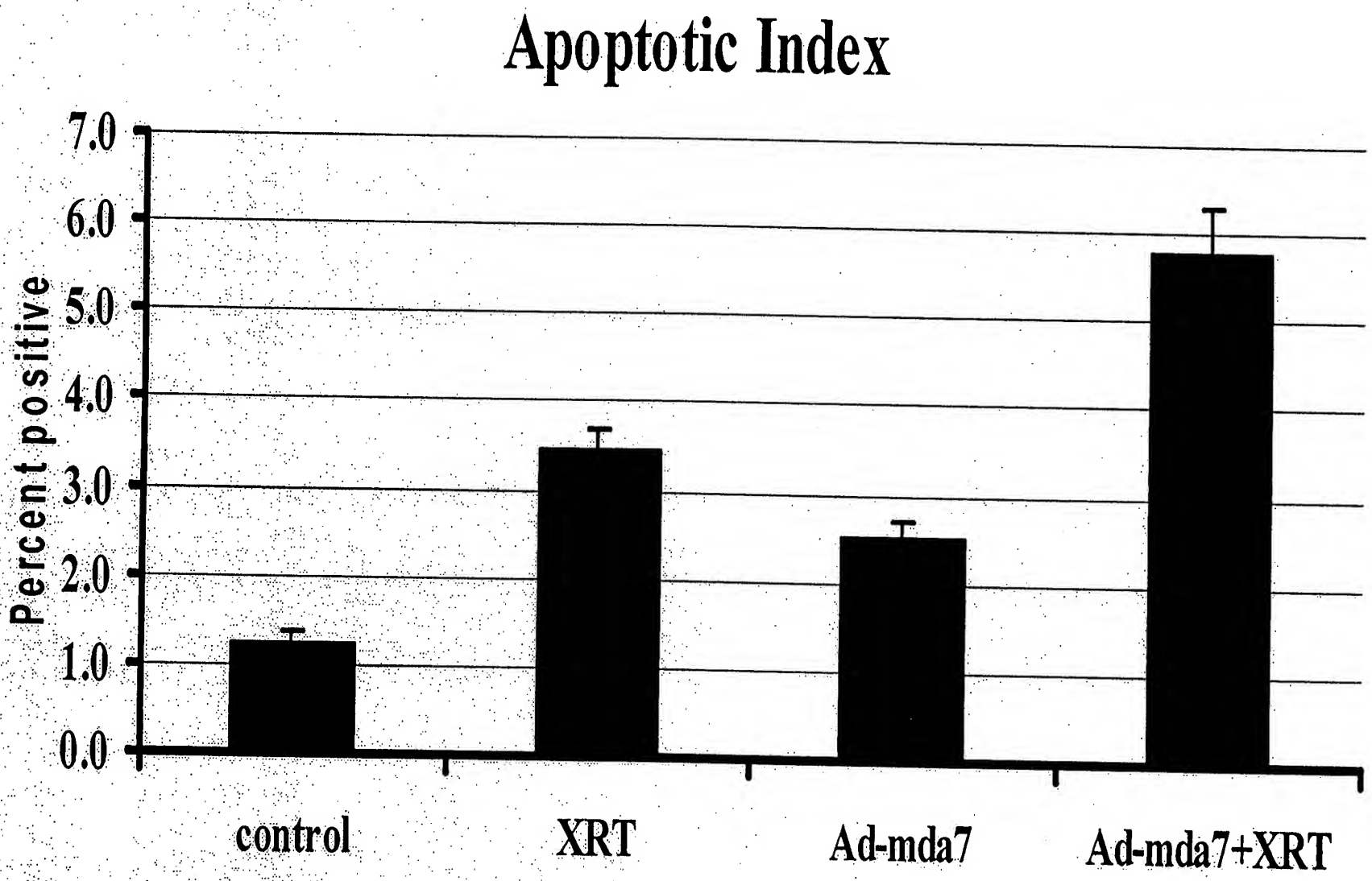

Apoptotic Index
Percent positive
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
control
XRT
Ad-mda7
Ad-mda7+XRT

FIG. 56

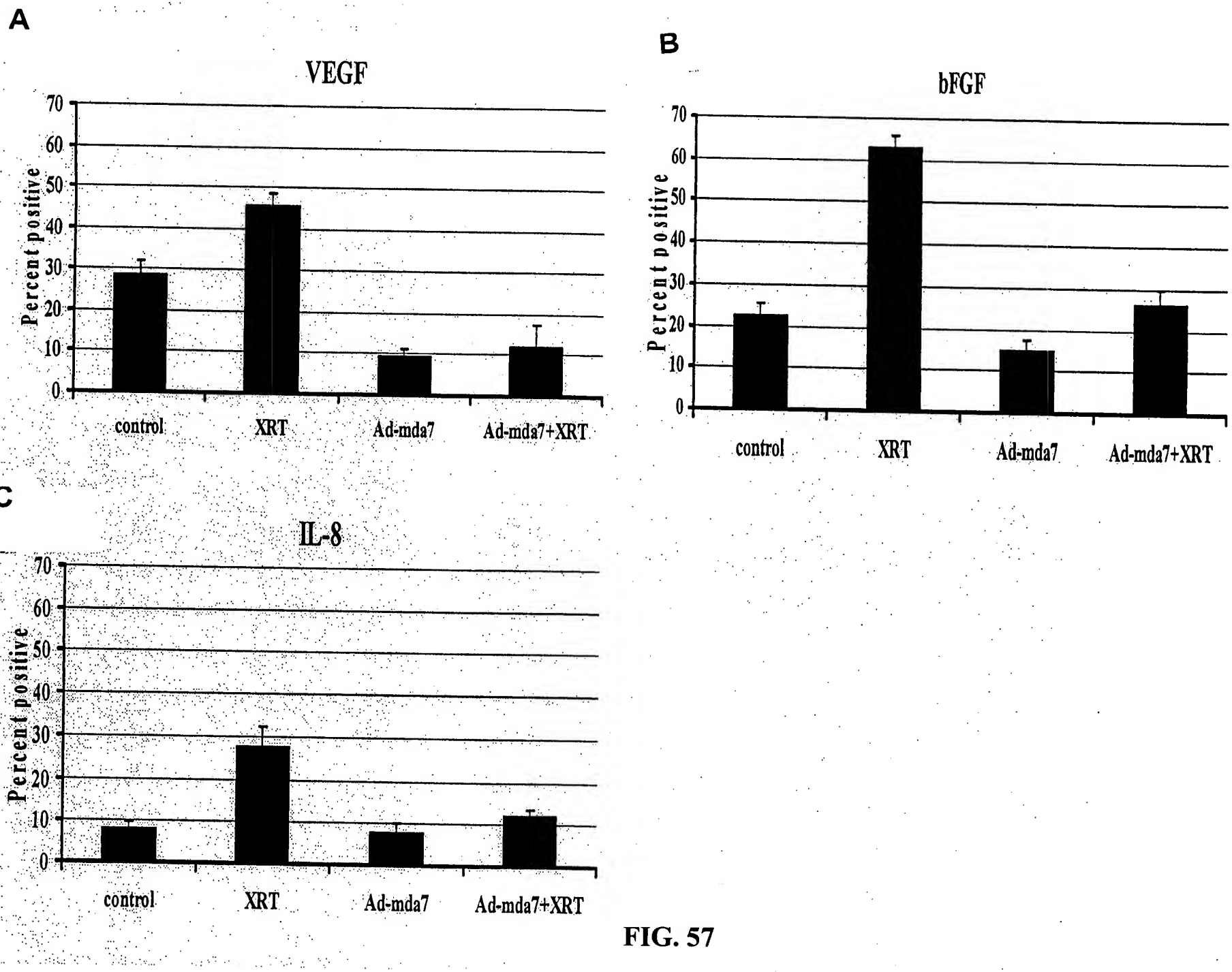

A
VEGF
Percent positive
70
60
50
40
30
20
10
0
control
XRT
Ad-mda7
Ad-mda7+XRT
B
bFGF
Percent positive
70
60
50
40
30
20
10
0
control
XRT
Ad-mda7
Ad-mda7+XRT
C
IL-8
Percent positive
70
60
50
40
30
20
10
0
control
XRT
Ad-mda7
Ad-mda7+XRT

FIG. 57

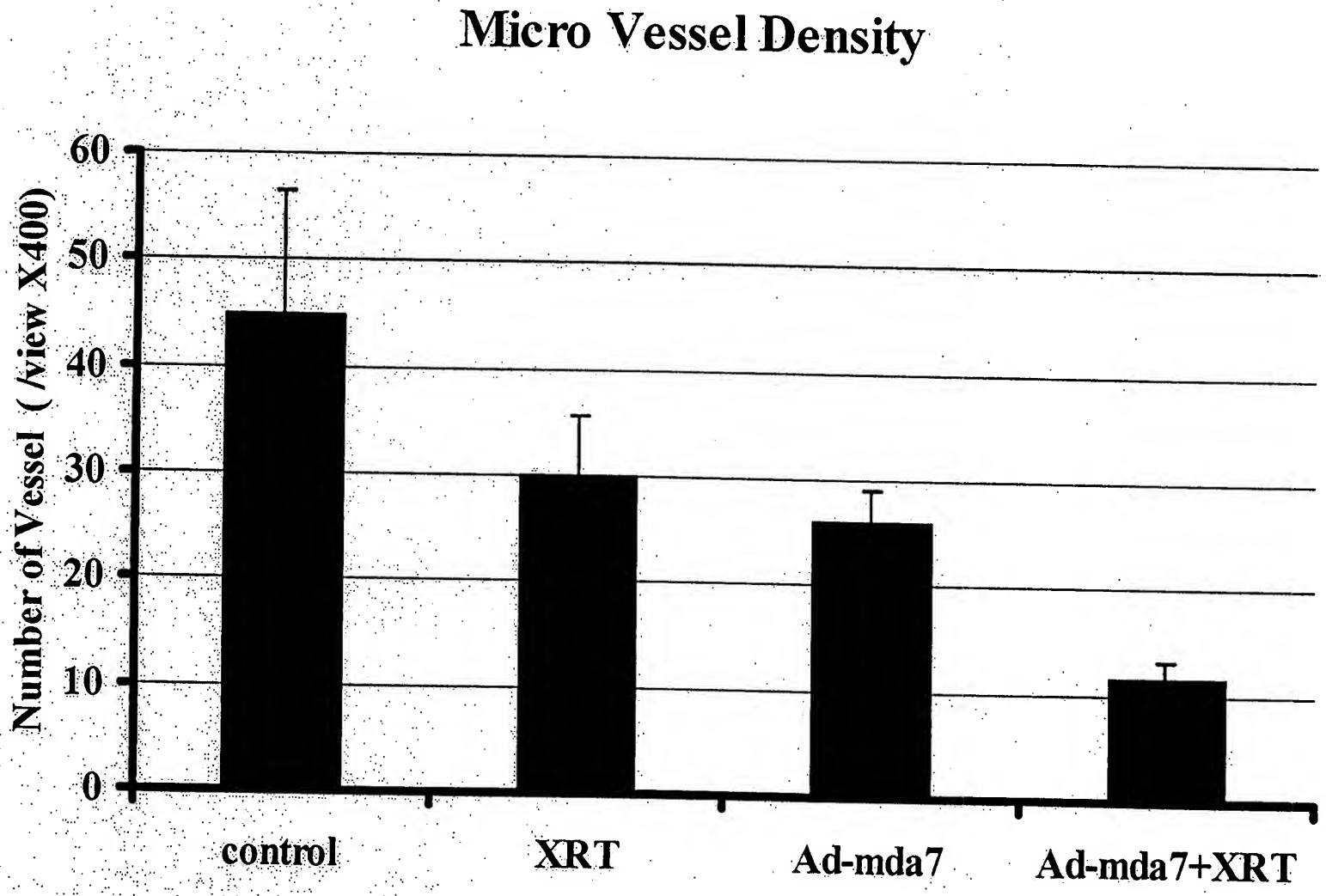

Micro Vessel Density
Number of Vessel (/view X400)
60
50
40
30
20
10
0
control
XRT
Ad-mda7
Ad-mda7+XRT

FIG. 58

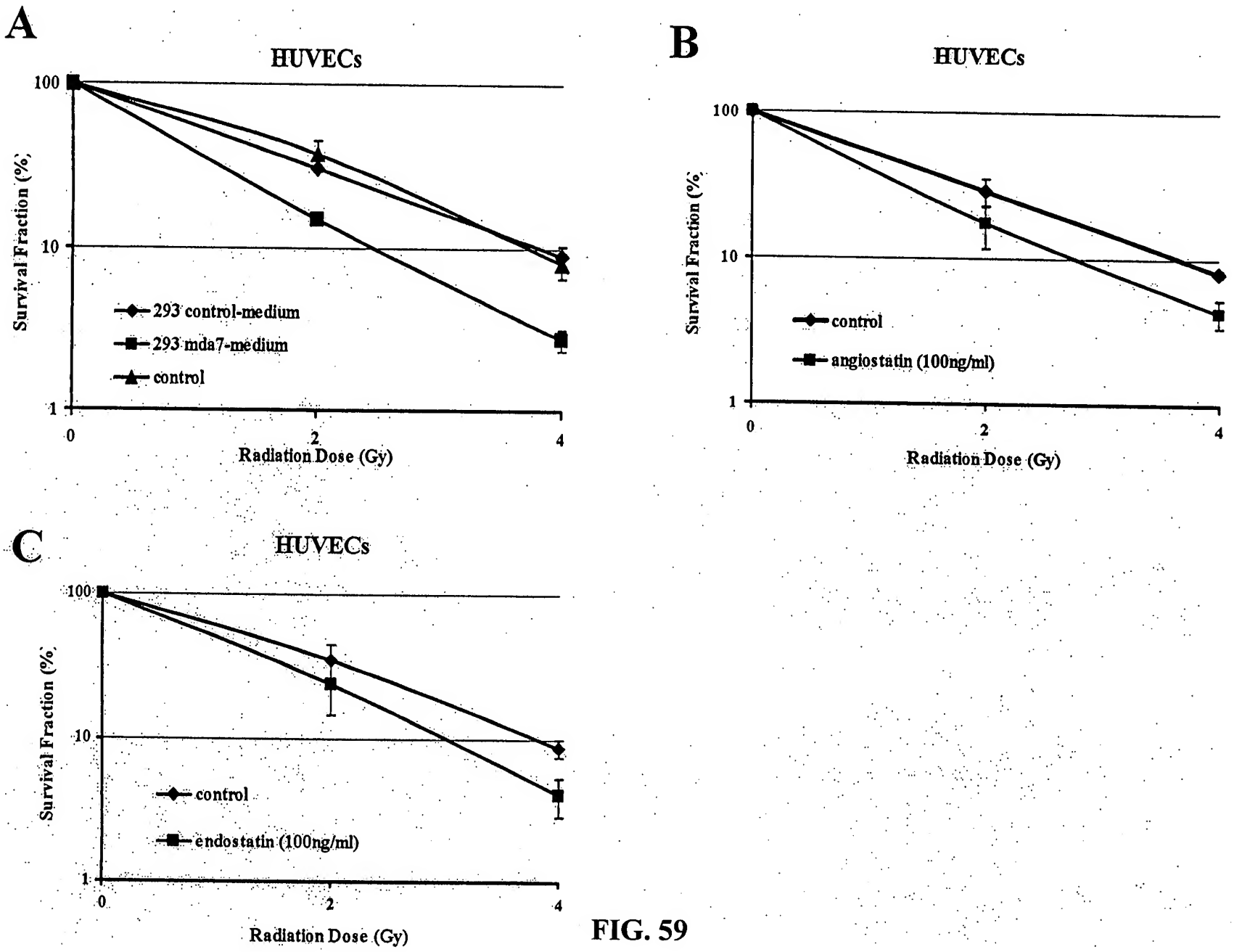

A
HUVECs
100
10
1
Survival Fraction (%)
293 control-medium
293 mda7-medium
control
0
2
4
Radiation Dose (Gy)
B
HUVECs
100
10
1
Survival Fraction (%)
control
angiostatin (100ng/ml)
0
2
4
Radiation Dose (Gy)
C
HUVECs
100
10
1
Survival Fraction (%)
control
endostatin (100ng/ml)
0
2
4
Radiation Dose (Gy)

FIG. 59

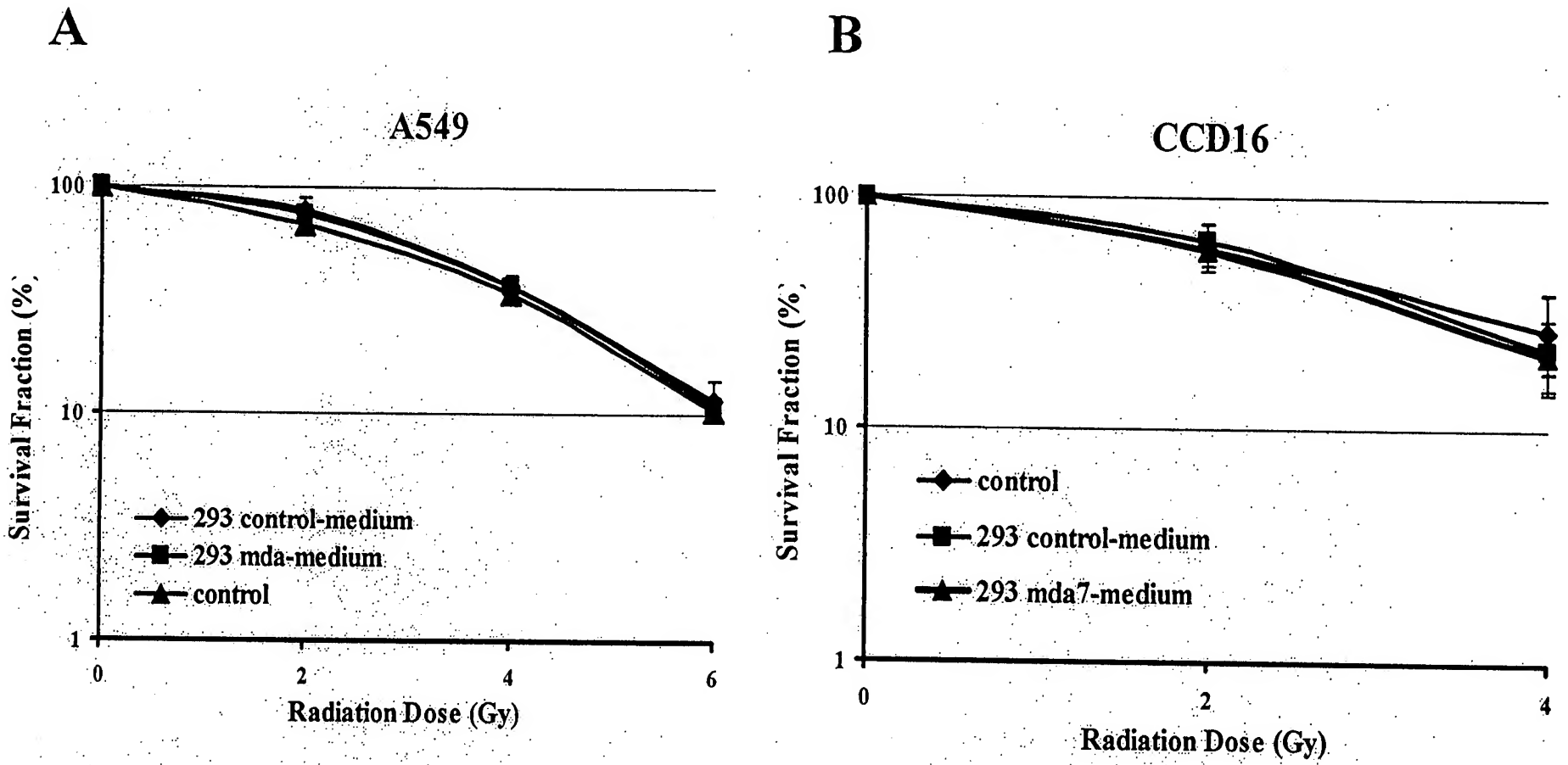

A
A549
100
10
1
Survival Fraction (%)
0
2
4
6
Radiation Dose (Gy)
293 control-medium
293 mda-medium
control
B
CCD16
100
10
1
Survival Fraction (%)
0
2
4
Radiation Dose (Gy)
control
293 control-medium
293 mda7-medium

FIG. 60

Targeting Plasmid Constructs

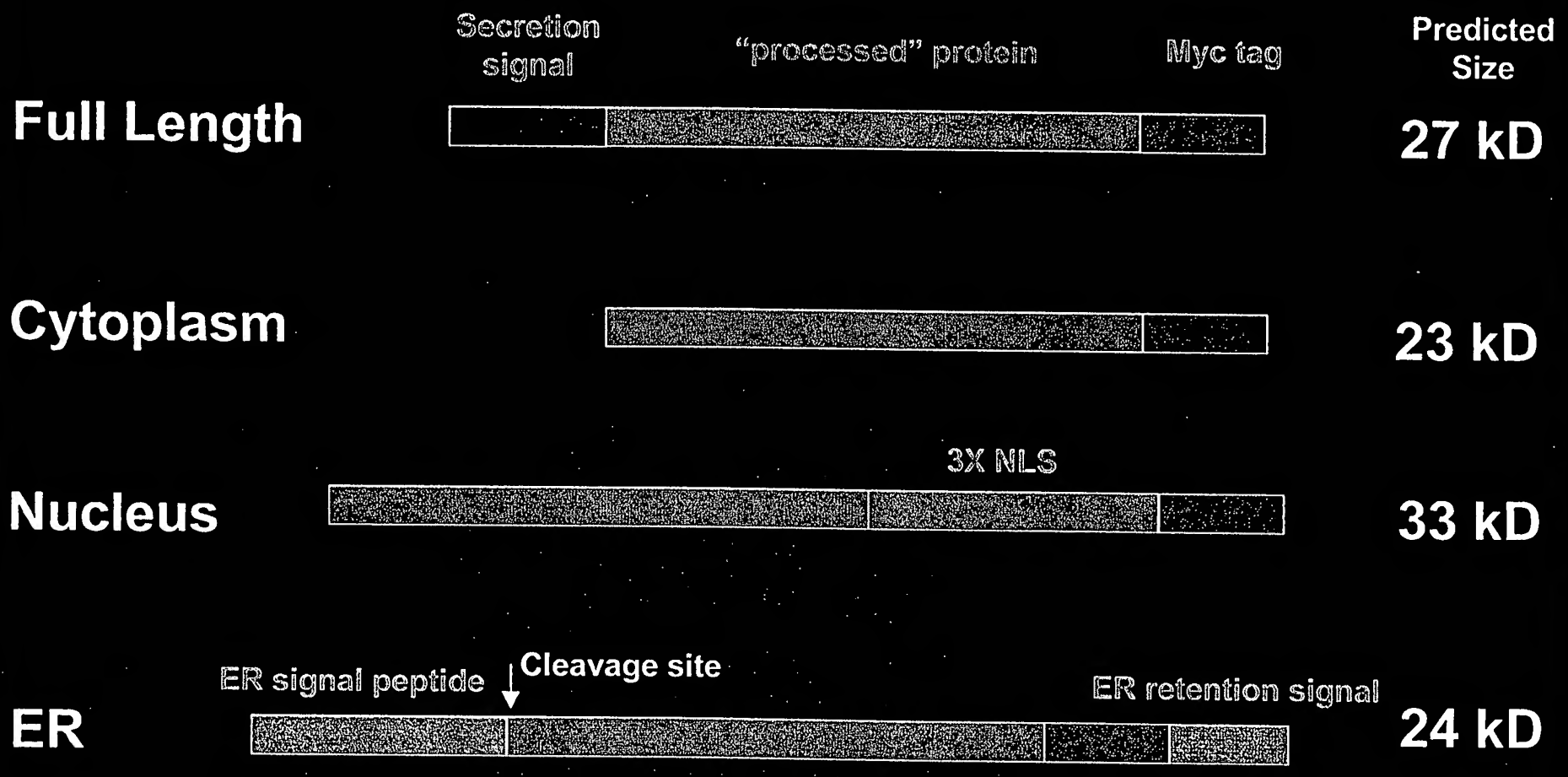


FIG. 61

ER Targeting of MDA-7 Blocks Colony Formation

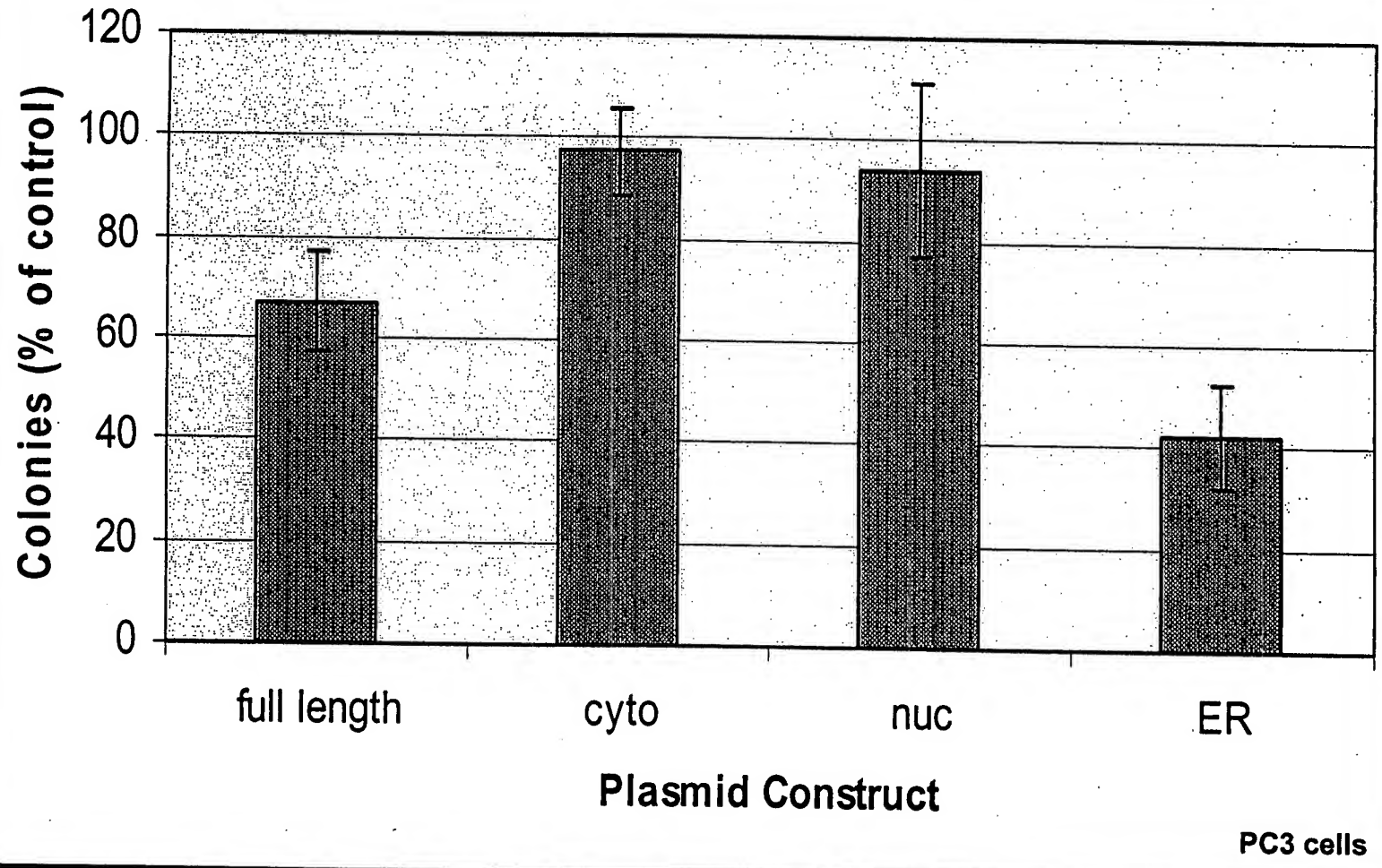


FIG. 62

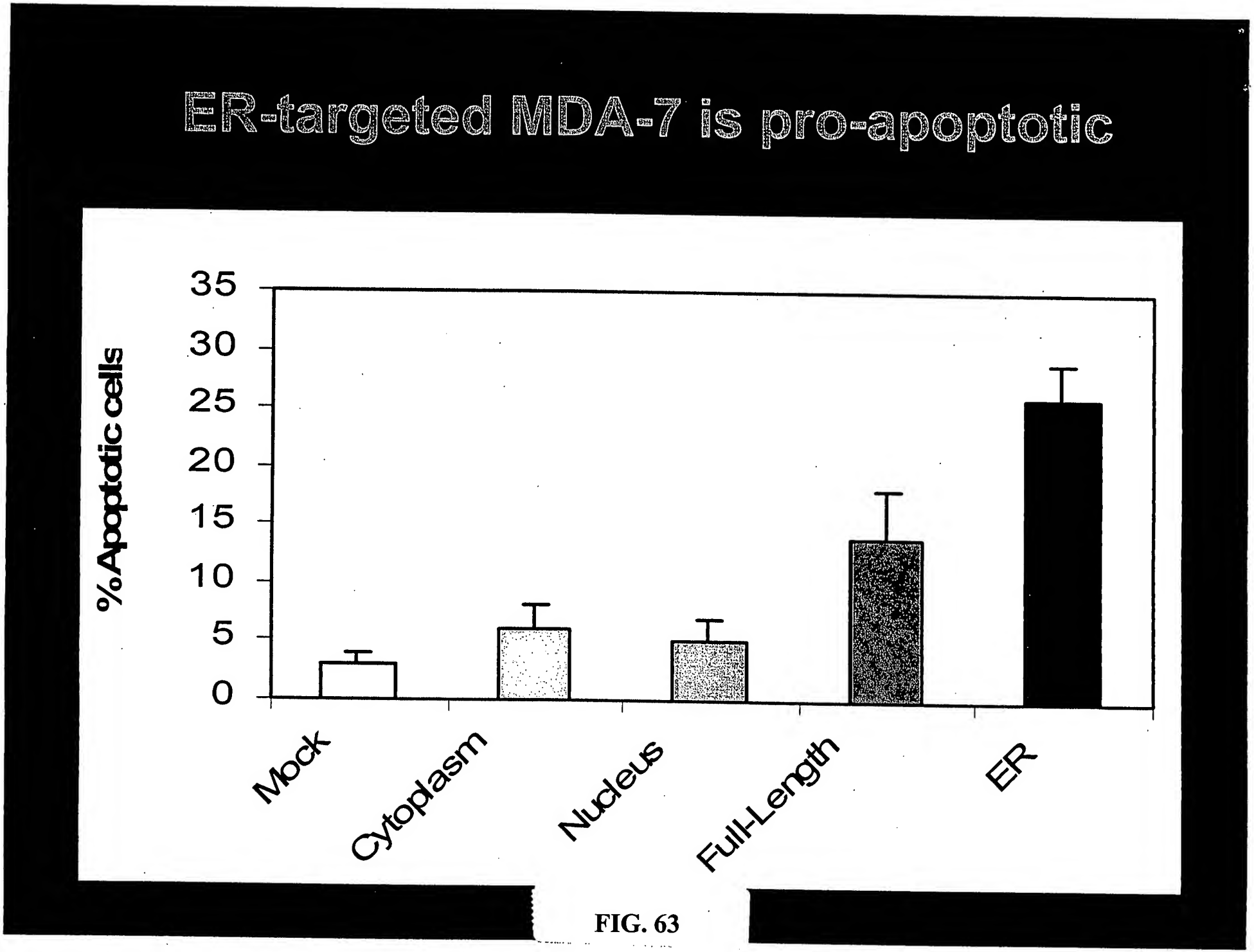

ER-targeted MDA-7 is pro-apoptotic
%Apoptotic cells
35
30
25
20
15
10
5
0
Mock
Cytoplasm
Nucleus
Full-Length
ER

FIG. 63

Inhibition of human ovarian cancer cell proliferation by Ad-mda7

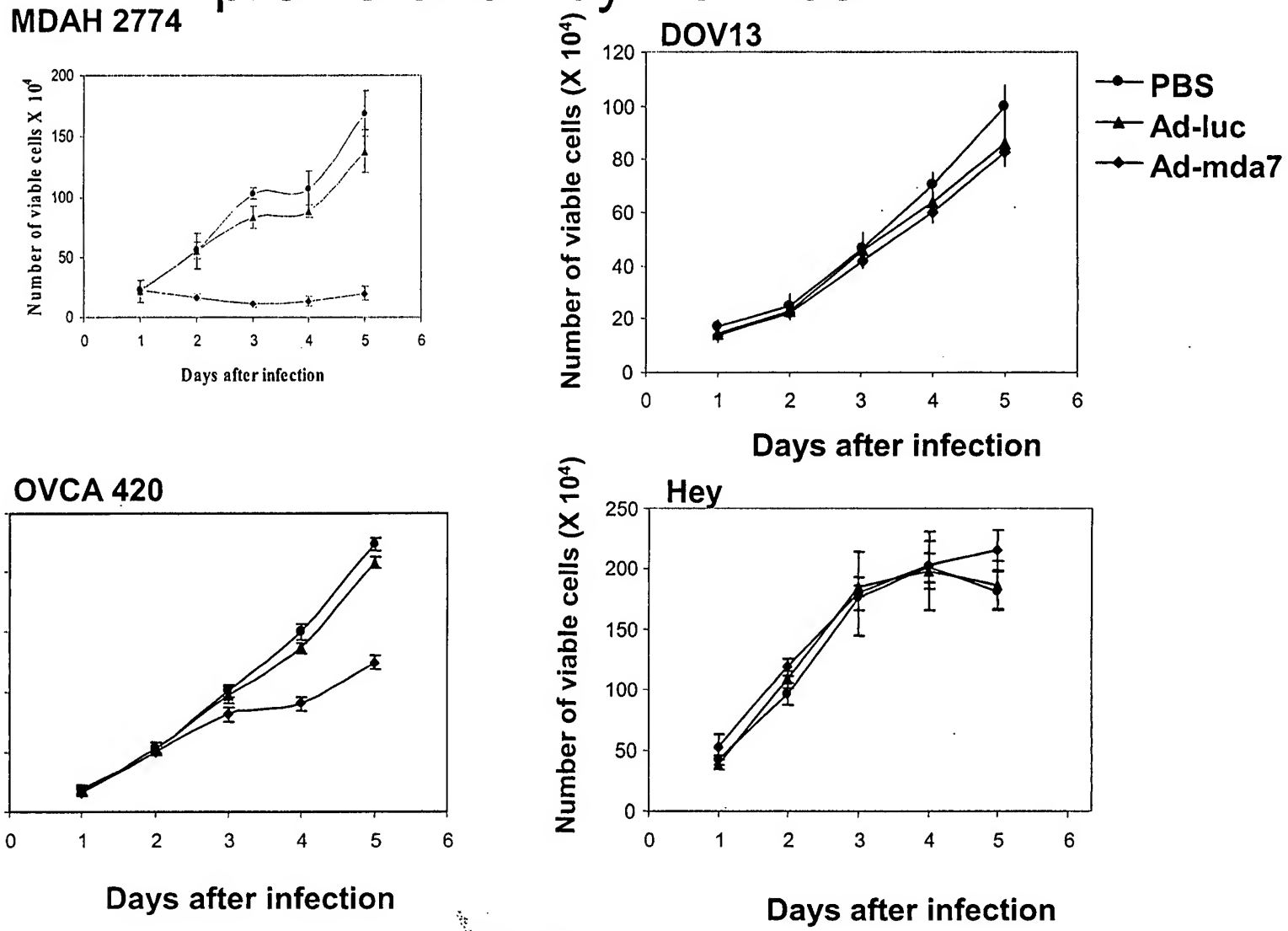


FIG. 64

Induction of cell cycle arrest by MDA-7 (MDAH 2774)

	G1	S	G2M	Apoptosis Sub G0
24 hrs				
PBS	30.55	34.55	34.9	2.05
Ad.Luc	32.95	36.6	30.45	1.41
Ad.mda-7	27.45	29.75	42.85	4
48 hrs				
PBS	40.8	32.6	26.6	0.955
Ad.Luc	28.75	32.45	38.8	0.84
Ad.mda-7	18.3	78	54.5	10.36

FIG. 65A

Ad-mda7 induced G2/M cell cycle arrest in OVCA 420

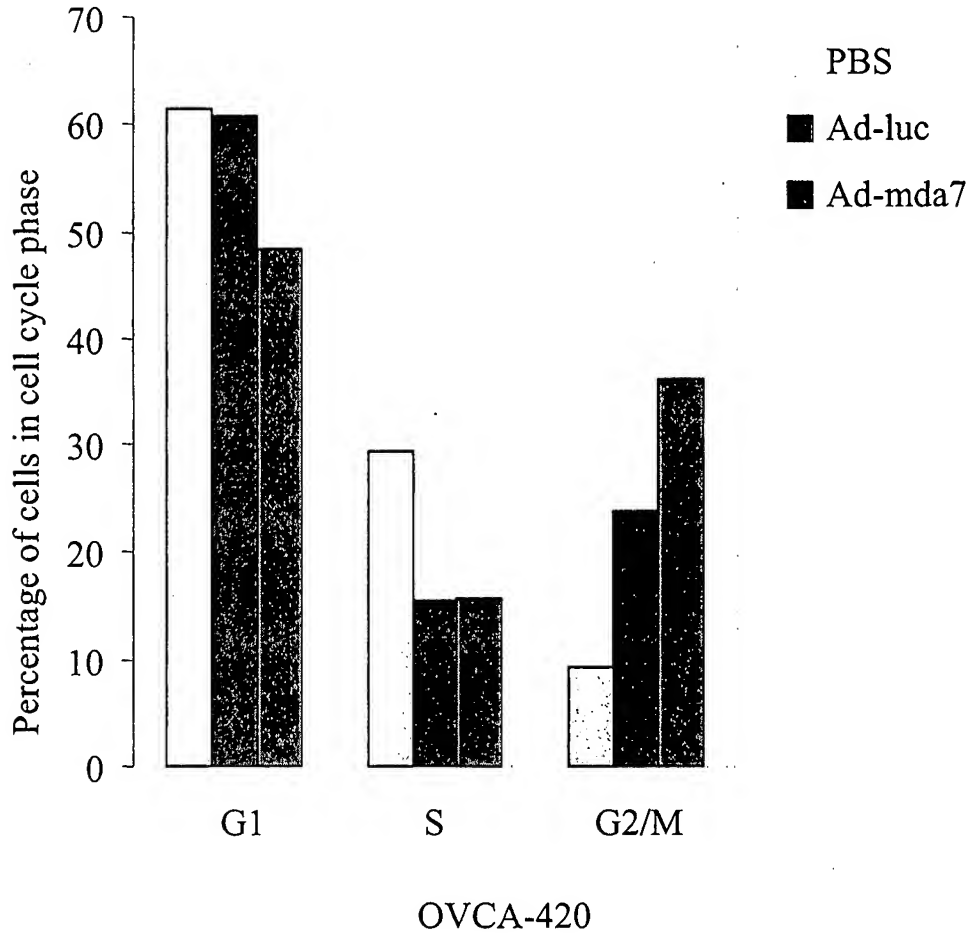


FIG. 65B

Induction of apoptosis due to overexpression of MDA-7 (MDAH2774)

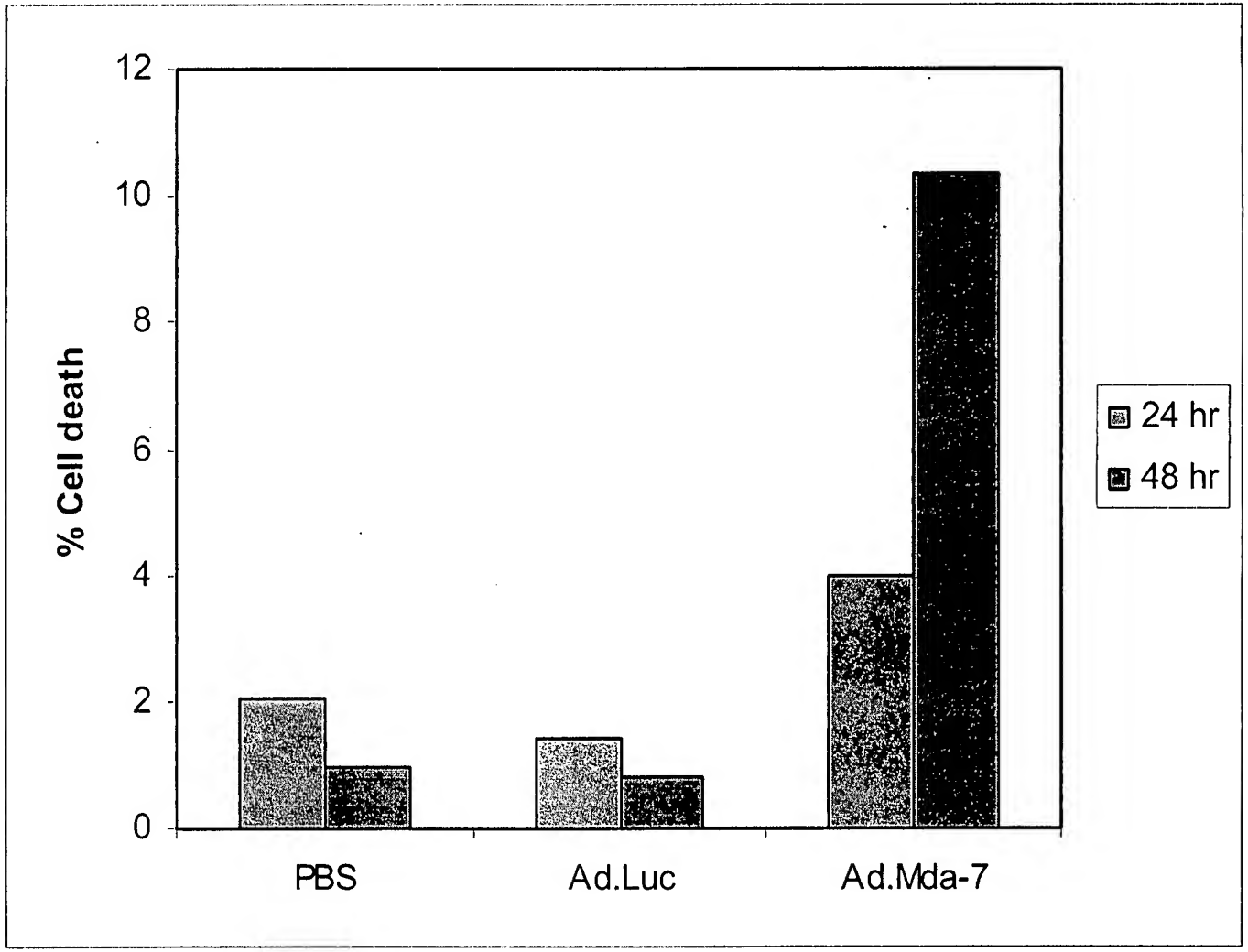


FIG. 66

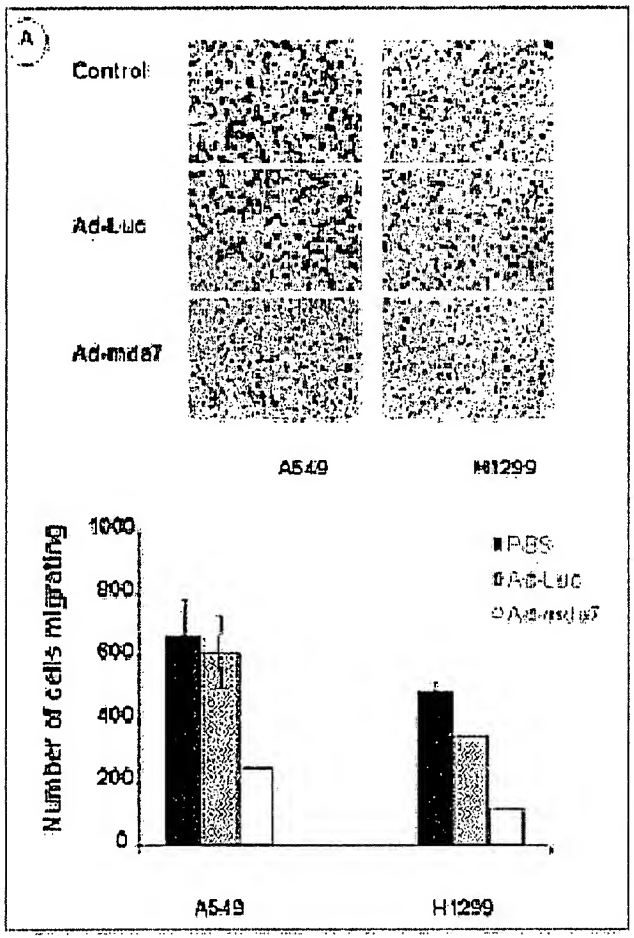


FIG. 67A

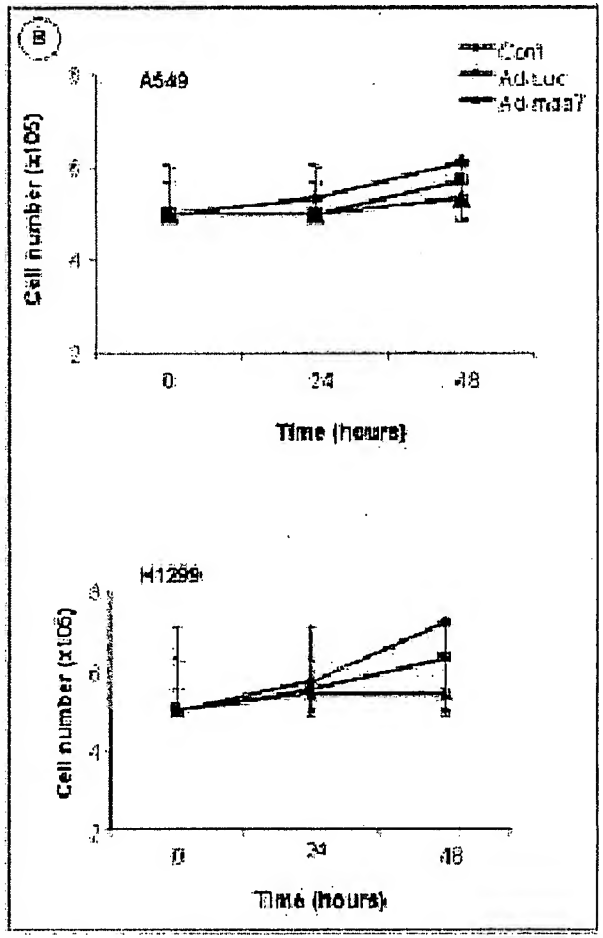


FIG. 67B

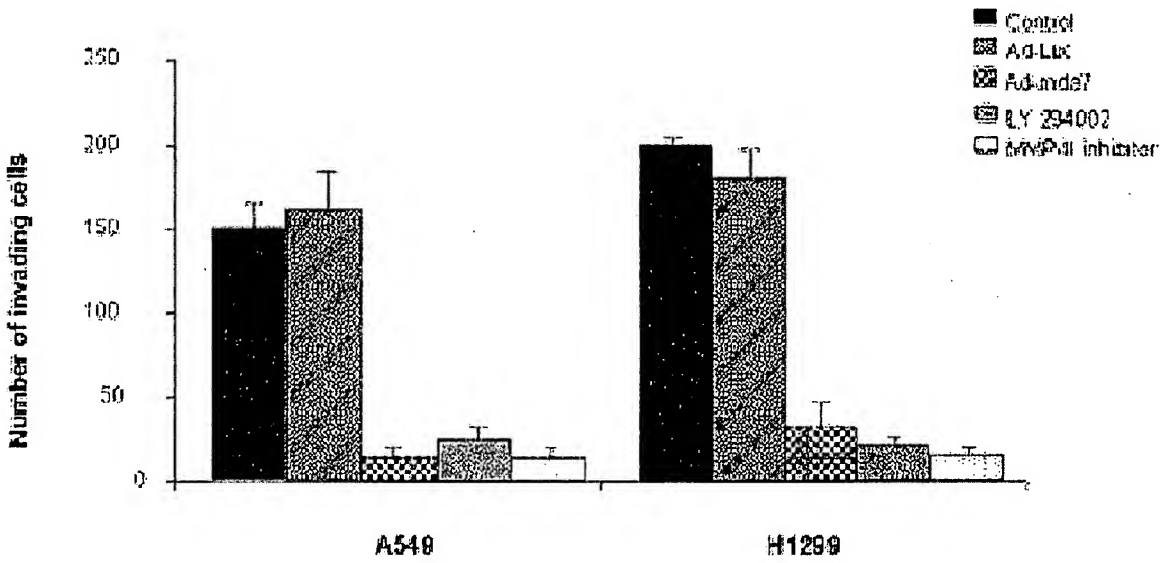

Control
Ad-Luc
Fulvestrant
LY 294002
MMP-II inhibitor
Number of invading cells
250
200
150
100
50
0
A549
H1299

FIG. 68

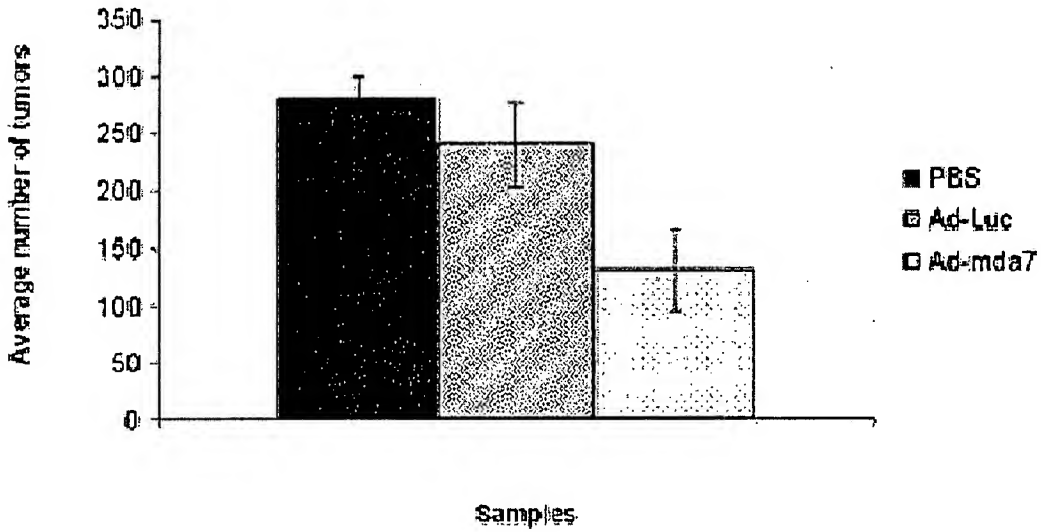

Average number of tumors
350
300
250
200
150
100
50
0
Samples
PBS
Ad-Luc
Ad-mda7

FIG. 69

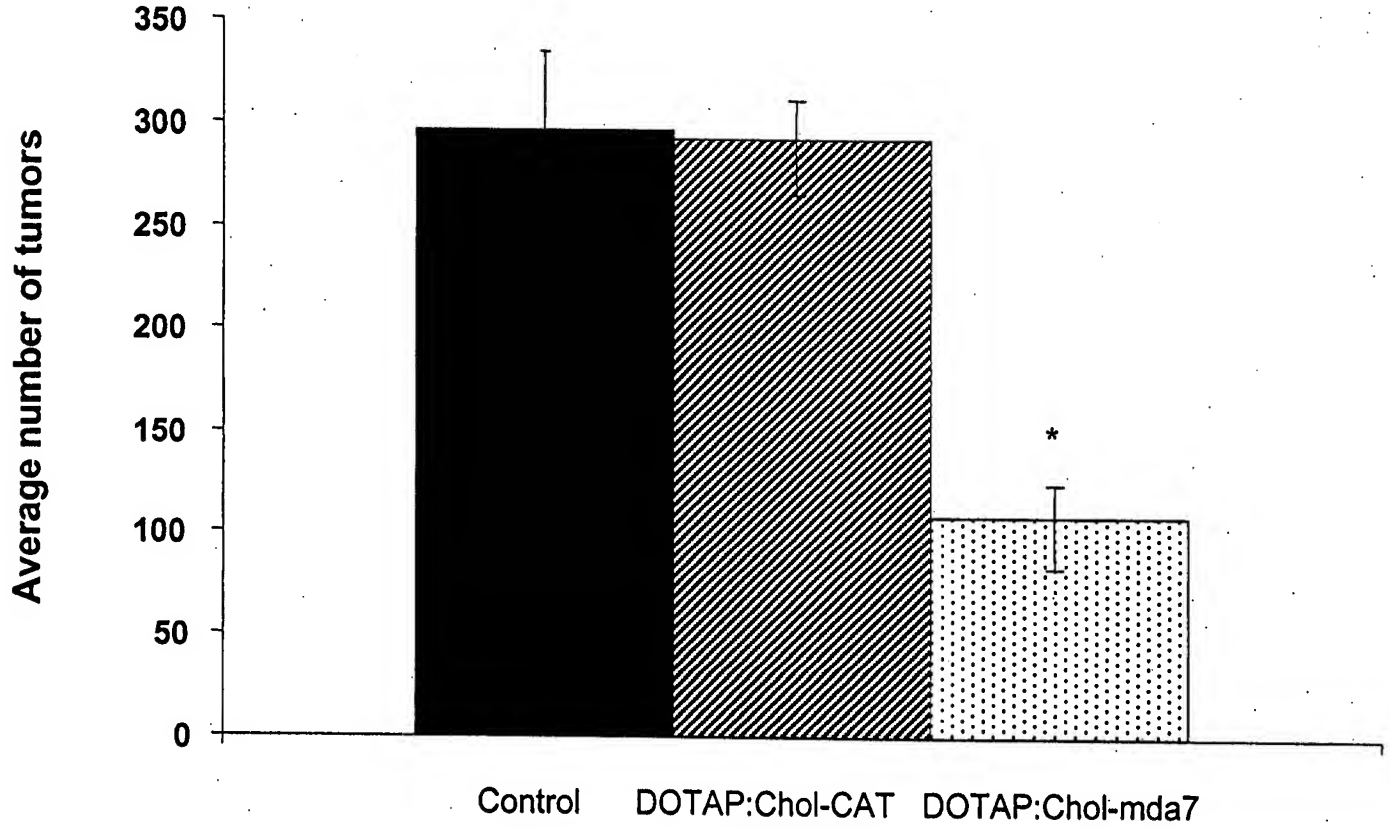

Average number of tumors
350
300
250
200
150
100
50
0
*
Control
DOTAP:Chol-CAT
DOTAP:Chol-mda7

FIG. 70

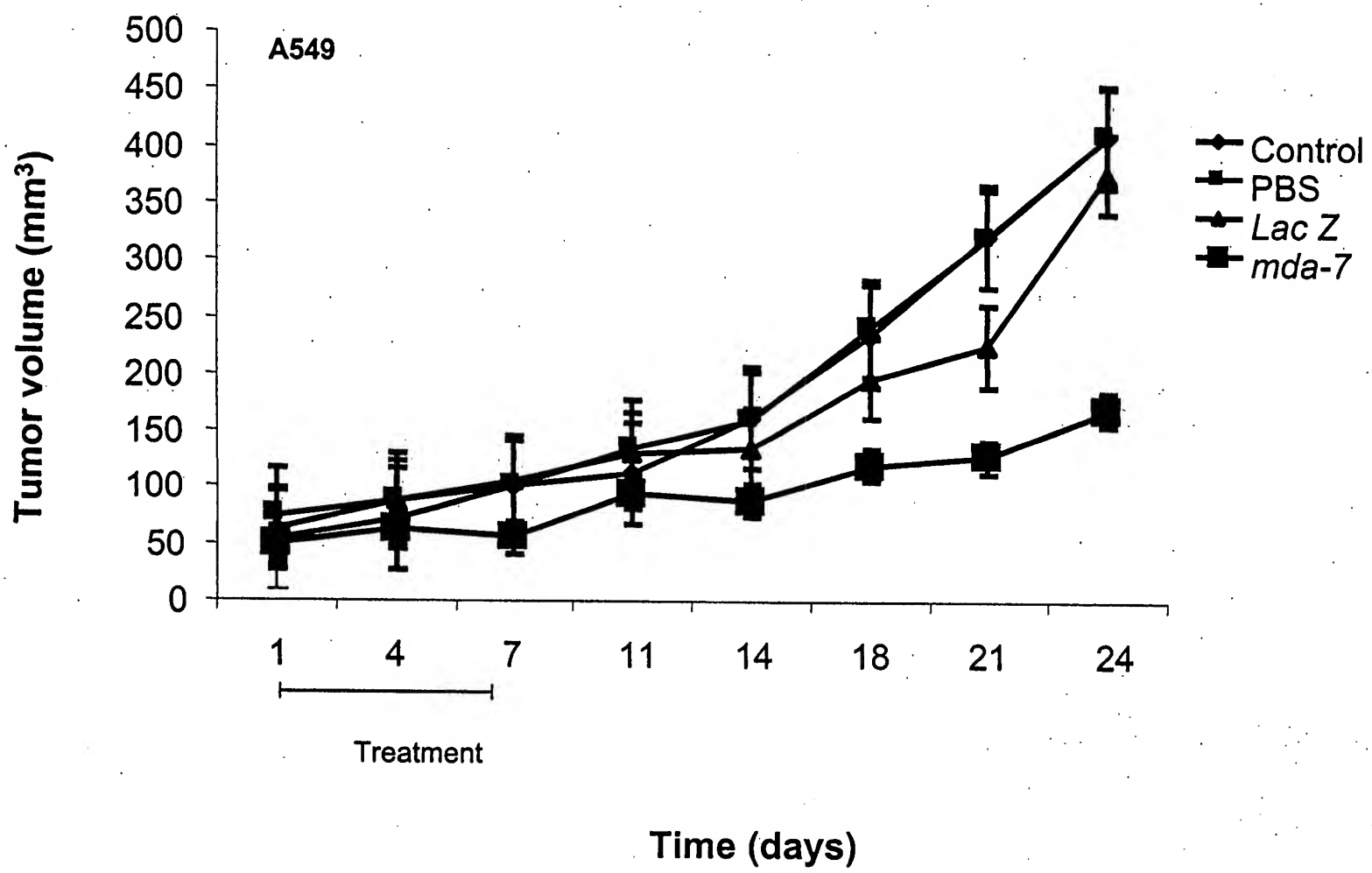

A549
Tumor volume (mm3)
500
450
400
350
300
250
200
150
100
50
0
1
4
7
11
14
18
21
24
Treatment
Time (days)
Control
PBS
Lac Z
mda-7

FIG. 71A

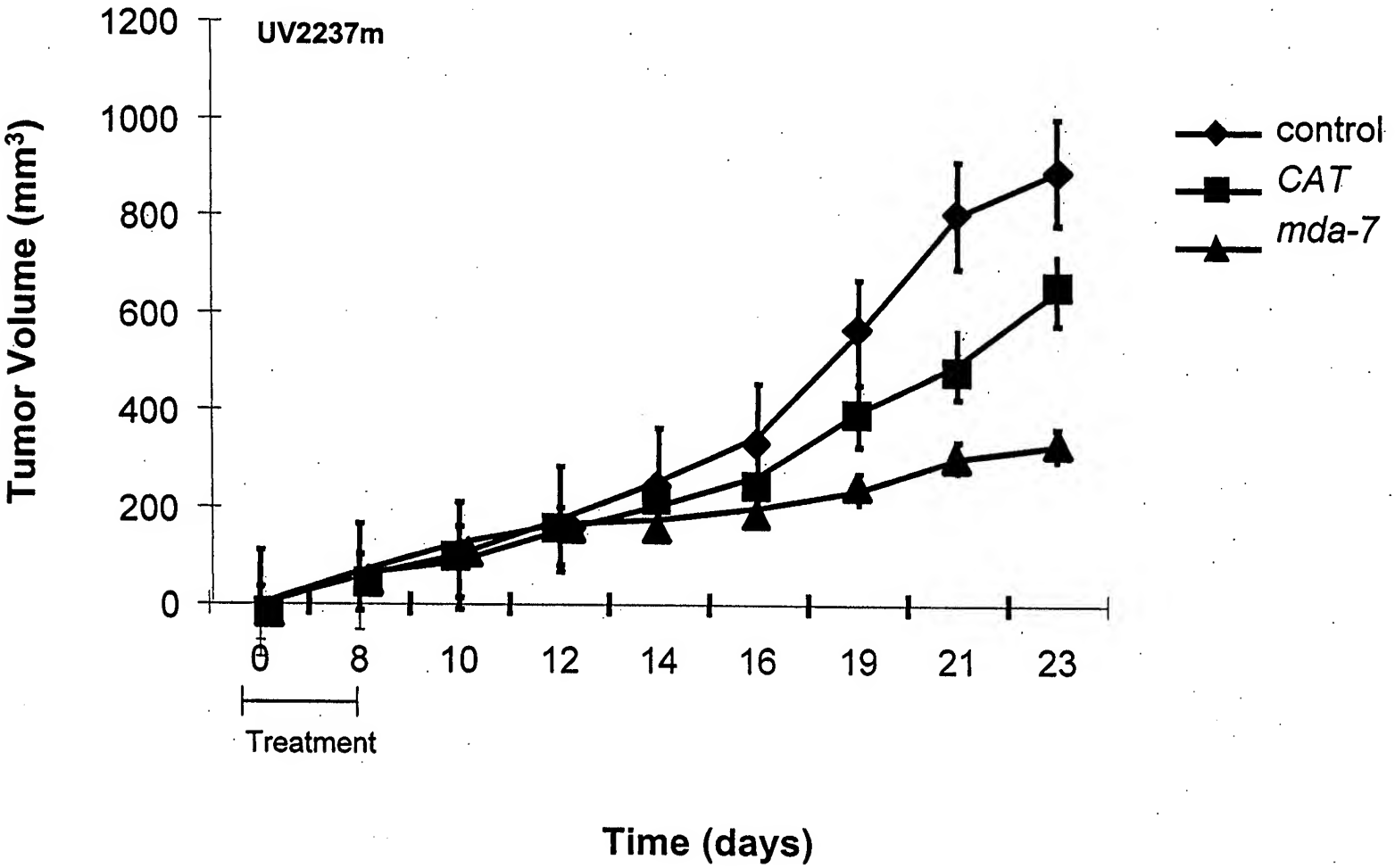

UV2237m
Tumor Volume (mm3)
1200
1000
800
600
400
200
0
0
8
10
12
14
16
19
21
23
Treatment
Time (days)
control
CAT
mda-7

FIG. 71B

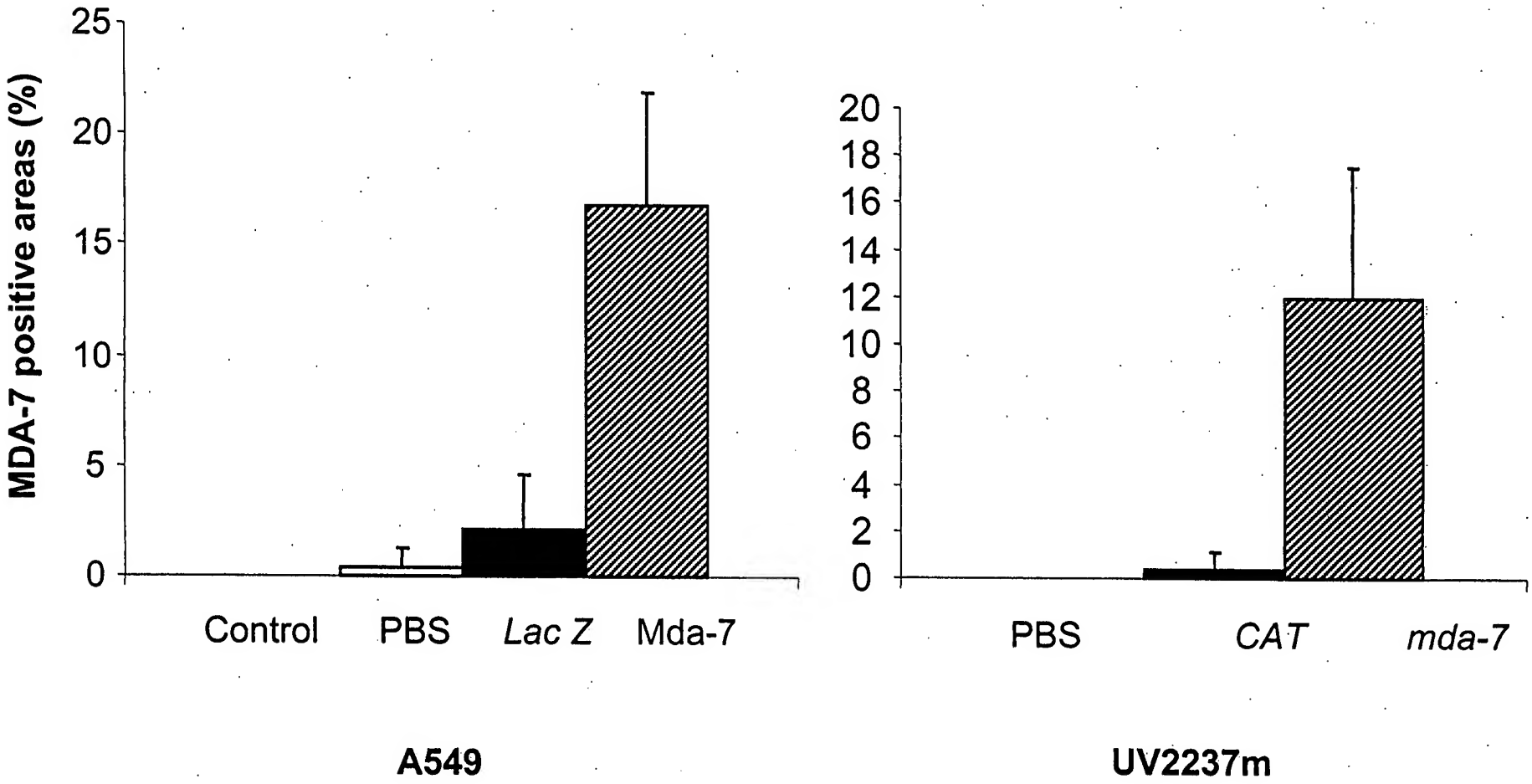

MDA-7 positive areas (%)
25
20
15
10
5
0
Control
PBS
Lac Z
Mda-7
A549
20
18
16
14
12
10
8
6
4
2
0
PBS
CAT
mda-7
UV2237m

FIG. 71C

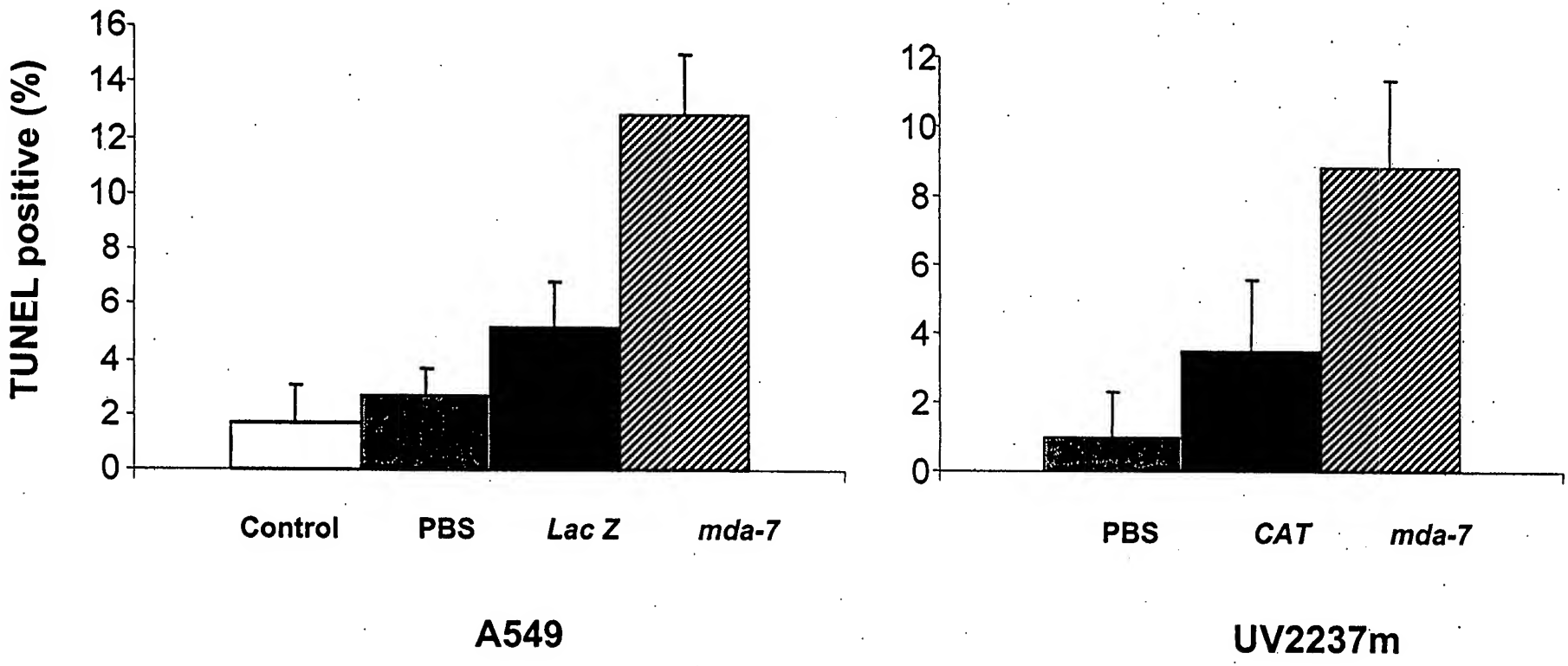

TUNEL positive (%)
16
14
12
10
8
6
4
2
0
Control
PBS
Lac Z
mda-7
A549
12
10
8
6
4
2
0
PBS
CAT
mda-7
UV2237m

FIG. 72

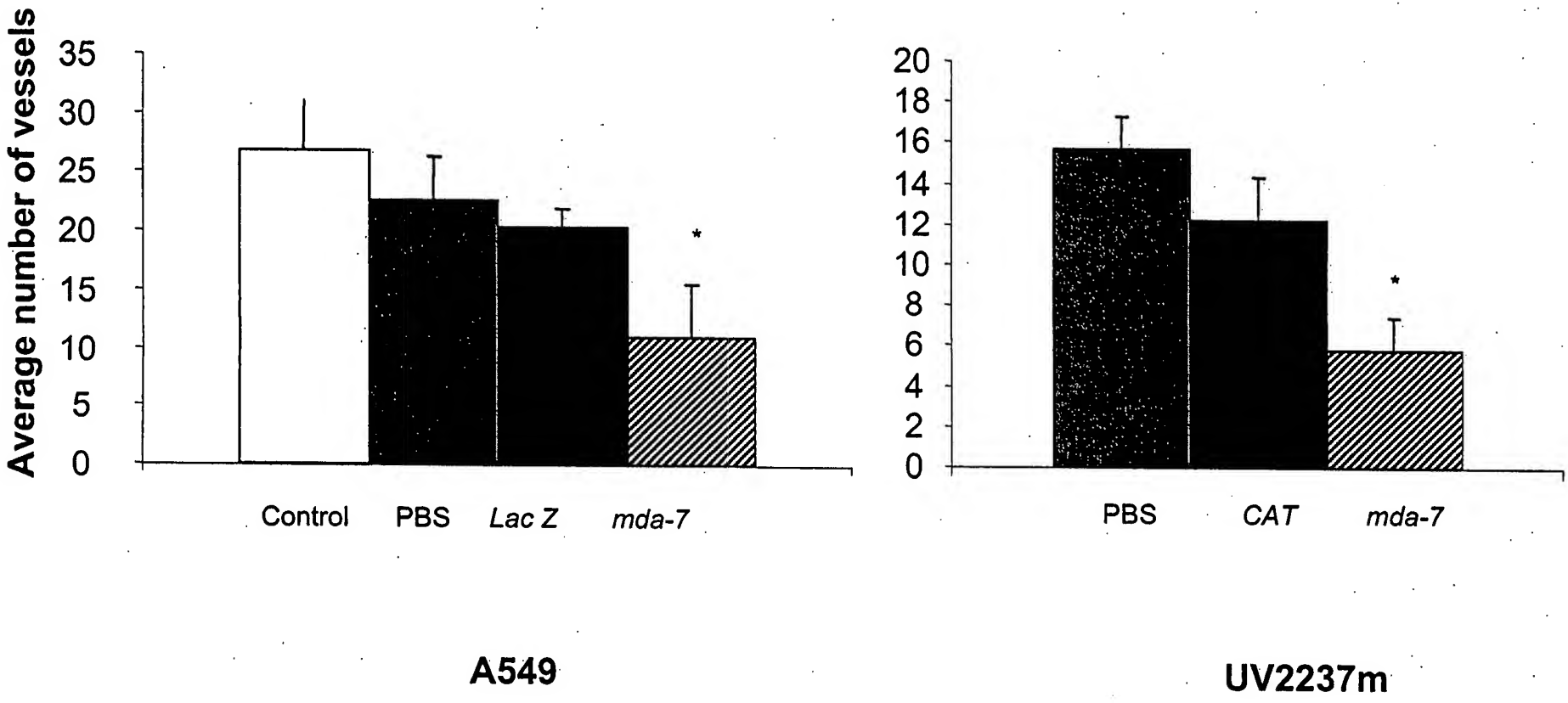

Average number of vessels
35
30
25
20
15
10
5
0
Control
PBS
Lac Z
mda-7
*
A549
20
18
16
14
12
10
8
6
4
2
0
PBS
CAT
mda-7
*
UV2237m

FIG. 73

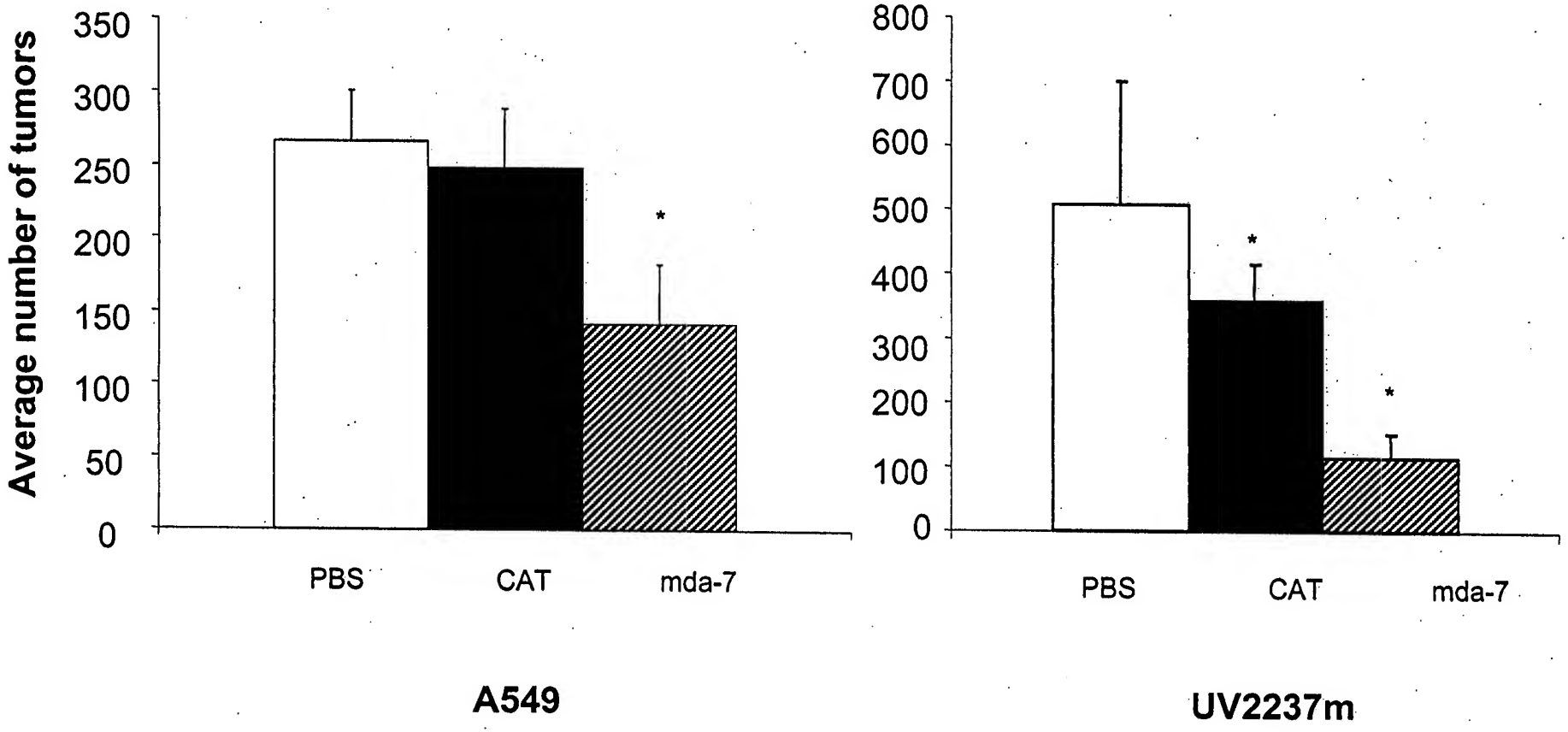

Average number of tumors
350
300
250
200
150
100
50
0
PBS
CAT
mda-7
*
A549
800
700
600
500
400
300
200
100
0
PBS
CAT
mda-7
*
*
UV2237m

FIG. 74

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